Edited by
Sam Wiseman
Sebastian Aspinall

50 LANDMARK PAPERS

every THYROID AND PARATHYROID SURGEON Should Know

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50 Landmark Papers

every

Thyroid and Parathyroid Surgeon Should Know

This book provides an expert perspective from some of the world's leading surgeons on the papers that have had the greatest impact in the field of thyroid and parathyroid surgery over recent years.

The broad range of topics covered will enable the reader to understand how recent research developments have led to changes in current thyroid and parathyroid surgical practice and represents an excellent resource for trainees at all levels preparing for specialty examinations.

This book contains:

- Concise review and analysis of key papers by expert clinicians, with each chapter focused on the most important aspects of the surgical management of thyroid and parathyroid disease
- Essential reading for students, residents, fellows, and surgeons studying for their professional exams or wanting an update on the current thyroid and parathyroid surgery literature
- Critical distillation of the diverse and expanding research over a broad range of topics from this field, including that includes investigation and management of benign and malignant thyroid disease; primary, secondary, and tertiary hyperparathyroidism; thyroid and parathyroid surgery; and surgical complications
- Expert analysis of the key contemporary papers and topics underlying the practice of endocrine neck surgery for general surgeons, otolaryngologists, head and neck surgeons, endocrine surgeons, trainees, and other healthcare professionals

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Typeset in Times
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To Natalie, Jacob, Isabel, Nicole, and my parents.

SAM

To Elspeth, Maisie, Jemima, John, and my mother.

SEBASTIAN

To mentors, teachers, colleagues, and trainees – past, present, and future.

SAM AND SEBASTIAN

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Preface

"Writers are the main landmarks of the past."

Edward Bulwer-Lytton

Recently, it was estimated that between 2016 and 2019 there were, on average, 367 surgical papers published daily, which is equivalent to approximately one paper every 4 minutes.[1] This exponential growth in the literature has occurred across all surgical specialties. Identifying the key papers that have had the greatest impact on the practice of thyroid and parathyroid surgeons represents a particular challenge. Not only do thyroid and parathyroid surgeons come from diverse specialty (general surgery and otolaryngology) and subspecialty (endocrine surgery, surgical oncology, head and neck surgery) backgrounds, practice in varied clinical settings, and treat a broad spectrum of disease, but the management of their patients is often complex and is usually multidisciplinary.

Awareness of the published papers that are most important to thyroid and parathyroid surgical practice in terms of their impact on patient management is critical. Nothing replaces an intimate knowledge of neck surgical anatomy, sound clinical judgment, training, experience, and meticulous surgical technique, but there are many exciting recent developments that have revolutionized the way thyroid and parathyroid operations are performed and also how the underlying diseases are managed. Employment of vessel sealing devices, intraoperative parathyroid hormone measurement, and utilization of recurrent laryngeal nerve monitoring technology are all examples of changes that have impacted current surgical practice. New approaches and developments continue to emerge, including parathyroid autofluorescence, remote access thyroidectomy, and robotic thyroidectomy, all of which show promise in continuing to transform the field.

The intention of the "50 Landmark Papers" series is to serve as a valuable resource by assisting busy clinicians, surgical trainees, and other healthcare professionals with identifying and interpreting the important literature in a specific surgical specialty or subspecialty. The aim of this book is to give surgeons and other healthcare professionals an expert overview of the landmark papers in thyroid and parathyroid surgical practice and a review of their underlying evidence. It will assist the practicing surgeon in "wading through" the expanding thyroid and parathyroid literature to find the "diamonds in the rough" or "landmark papers". We also believe this book will be especially helpful for trainees in preparing for their final surgical specialty or subspecialty certification examinations and healthcare professionals wanting to learn more about thyroid and parathyroid surgery.

Perhaps the most challenging part of putting this book together was determining what constituted a "landmark paper." To accomplish this we first created a comprehensive

list of 50 topics of interest to thyroid and parathyroid surgeons for inclusion in the book by review of the current literature, specialty and subspecialty texts, and expert opinion. Then we identified a diverse group of recognized experts in the field, who came from centers throughout the world and were willing to contribute chapters to the book. Remarkably, the 50 chapters in this book have a total of 101 authors from 64 centers located in 16 different countries. Specific topics were then assigned to each chapter author, who was then tasked with identifying its landmark paper. While ultimately landmark paper selection was subjective, some general guiding principles were applied. These included favoring more recent papers (those published since 2000); considering total and/or annual paper citations; avoiding review articles, editorials, commentaries, and most guidelines; excluding papers not published in English or in peer-reviewed journals; avoiding retracted or duplicate papers; and preferring papers relevant to current clinical practice, those referenced by national guidelines, and those that provide a high scientific level of evidence. Once chosen by the chapter authors, with input from the editors and feedback from other chapter authors (who were made aware of all landmark paper selections but blinded to the identity of the chapter authors), the landmark paper selection was finalized. To limit bias, the editors discouraged chapter authors from selecting landmark papers that they had authored themselves except in exceptional circumstances. In the end a wide variety of types of landmark papers were chosen that we consider best addressed the key topics covered in the book. Remarkably, and to their credit, all the invited authors completed their assigned chapters, and none defaulted.

There will inevitably be surgeons and other healthcare professionals who disagree with the choice of some of the selected landmark papers, though the chapters all present a discussion of other relevant literature in the subject area to ensure a balanced review of the specific topic. In the future, as surgical practice continues to progress, new landmark papers will emerge and older papers will be confined to historical interest. We believe that the landmark papers selected for inclusion in this book are important not only because of their current impact but also because of the insight they provide into the discourse of modern surgical practice, and thus they are a testament to the intelligence and creativity of the thyroid and parathyroid surgeons and others who are their contributors.

Sam M. Wiseman
Sebastian Aspinall

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Chapter 1

Ultrasound

Review by Julia E. Noel and Lisa A. Orloff

Landmark Paper

THYROID IMAGING REPORTING AND DATA SYSTEM FOR US FEATURES OF NODULES: A STEP IN ESTABLISHING BETTER STRATIFICATION OF CANCER RISK

Kwak JY, Han KH, Yoon JY, Moon HJ, Son EJ, Park SH, Jung HK, Choi JS, Kim BM, Kim EK. *Radiology*. 2011;260(3):892–899.

RESEARCH QUESTION/OBJECTIVES

The widespread use of ultrasonography (US) has led to the increased detection of thyroid nodules that are highly prevalent in the global adult population. However, the vast majority (90% or greater) of nodules are benign and may not require biopsy or intervention. As recognition of specific sonographic features associated with malignancy has progressed, the need for a standardized reporting system for ultrasound findings combined with a risk stratification mechanism has also grown. The objective of this landmark paper[1] is to develop a practical, user-friendly Thyroid Imaging Reporting And Data System (TI-RADS) by which to classify, report, and stratify thyroid nodules for risk of malignancy and the need for fine-needle aspiration biopsy (FNAB).

STUDY DESIGN

This is a retrospective cohort study of thyroid nodules that underwent surgery and/or FNAB as well as real-time US at Yonsei University College of Medicine in Korea between May and December 2008. US features were categorized by **internal component** (solid or mixed solid/cystic); **echogenicity** (hyperechoic, isoechoic, hypoechoic, or markedly hypoechoic); **margins** (well-circumscribed, microlobulated, or irregular); **calcifications** (microcalcifications, macrocalcifications); and **shape** (taller than wide or wider than tall in transverse view).

SAMPLE SIZE

In total, 1,658 nodules were reported to be from a population of 3,414 consecutive patients with thyroid nodules who underwent a total of 3,674 (FNABs) and/or follow up.

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INCLUSION/EXCLUSION CRITERIA

All nodules with US data, a maximum diameter of at least 1 cm, and either benign or malignant cytology results by FNAB, or pathology results from surgery performed for non-definitive cytology (either suspicious for papillary thyroid carcinoma, indeterminate, or inadequate), were included in the study population. Nodules were excluded if they did not meet size criteria or if they did not undergo surgery despite non-definitive cytology results. The study did include some minors (<18 years old) and some patients with more than one nodule.

INTERVENTION OR TREATMENT RECEIVED

Real-time US examination and US-guided FNAB were performed, and nodules were characterized according to their internal component, echogenicity, margins, calcifications, and shape. Features considered suspicious were microcalcifications, irregular or microlobulated margins, marked hypoechogenicity, and taller-than-wide shape. Mixed cystic and solid nodules were evaluated based on their solid internal components. US-guided FNABs were analyzed by smears with Papanicolaou staining and cell block processing. Multivariate logistic regression analysis with generalized estimating equations was performed to determine the independent US features predictive of malignancy. Scores for each significant predictor were multiplied by their beta coefficient to enable a comparison of the magnitude of effect; and the linear association between the number of suspicious features and the probability of malignancy was evaluated.

RESULTS

Of the 1,658 nodules included, 275 (16.6%) were malignant (238 confirmed by surgical pathology and 37 confirmed by cytology). By univariate analysis, the US features significantly associated with malignancy were solid, hypoechoic, markedly hypoechoic, irregular margins, microcalcifications, and taller-than-wide shape. By multivariate analysis, the risk of malignancy increased as the number of suspicious US characteristics increased. The US nodule feature with the highest risk of malignancy was the presence of a microlobulated margin followed by microcalcifications, both of which were considered to be of a higher risk than the combination of solid and hypoechoic. Based on these analyses, the authors created TI-RADS categories, modeled after the precedent of Breast Imaging Reporting And Data System (BI-RADS),[2] as follows: Thyroid Imaging Reporting And Data System (TI-RADS) 3 (no suspicious US features); TI-RADS 4a, 4b, and 4c (one, two, and three or four suspicious US features, respectively); and TI-RADS 5 (five suspicious US features). These categories were associated with an increasing risk of malignancy, with a TI-RADS 3 lesion carrying a 1.7% risk; 4a, b, and c with 3.3%, 9.2%, and 44.4–72.4% risk, respectively; and a TI-RADS 5 lesion carried an 87.5% risk of malignancy. Acknowledging the first use of the "TI-RADS" terminology by Horvath et al.,[3] as well as a prior attempt by Park et al.[4] to create an equation for predicting the probability of malignancy based on US features, the authors attempted to create a new, practical, and convenient TI-RADS that would allow for **standardization of reporting** of thyroid US, as well as establish criteria to **minimize unnecessary biopsies** of

thyroid nodules. Emphasis on the ability to count the number of suspicious US features was intended to simplify the clinical application of TI-RADS in the field. Subsequent studies have supported the validity and reproducibility of the TI-RADS system,[5,6] while expanding the basis for categorization of nodules to include larger overall numbers and types of pathology.

STUDY LIMITATIONS

This was a single-institution study (albeit with seven participating radiologists) that had follow-up data on only a subset of their population, resulting in a potential selection bias. Real-time imaging was not included; rather, previously captured images were reviewed retrospectively. Some thyroid nodules did not undergo surgery but had cytology (thyroid) results only. Furthermore, only nodules that underwent US-guided FNAB were included, meaning they were either suspicious nodules or the largest non-suspicious nodule in a multinodular gland. The fitted probability of malignancy for each suspicious US feature in this study had a wide range, reducing overall specificity and sensitivity. The overwhelming majority of patients in the study with malignancy (95%) had papillary thyroid carcinoma, limiting the application of TI-RADS to other malignant histological diagnoses. Also, the use of BI-RADS categories to stratify thyroid nodules into TI-RADS categories oversimplified the similarities between breast and thyroid cancers, which can behave very differently. Of note, this landmark paper also predated the implementation of the Bethesda System for reporting thyroid cytopathology,[7] a contemporary, parallel advancement in reporting and communication regarding thyroid nodular disease.

STUDY IMPACT

This paper represents a landmark study, among a host of important investigations, that has aided in the movement to develop a common language for reporting suspicious and non-suspicious thyroid US features and guide decisions about when to biopsy thyroid nodules. Along with refinement in US resolution has come progressive sophistication in pattern and feature recognition. A generation of thyroidologists has come to realize the need to avoid excessive diagnosis and intervention for potential or even real but indolent thyroid cancers, while avoiding under-recognition and under-treatment of aggressive thyroid malignancies. The most prominent such “risk stratification systems” in current use include the American Thyroid Association (ATA) guidelines system[8] and the American College of Radiology (ACR) TI-RADS system,[9] but globally there are similar systems including the Korean K TI-RADS,[10] European Union (EU) TI-RADS,[11] American Association of Clinical Endocrinologists (AACE), American College of Endocrinology (ACE) and Associazione Medici Endocrinologi (AME) guidelines,[12] British Thyroid Association guidelines,[13] and Chinese C TI-RADS.[14] Though based upon similar US features, these systems were developed in different patient populations and vary in emphasis upon each feature in determining the risk of malignancy and, therefore, in sensitivity and specificity.[15] Even so, nodules assigned to each category within any of these systems are associated with a range of risks rather than a precise risk of malignancy, especially for indeterminate nodules, owing to their prospective application in diverse practices.[16] Similarly, each system establishes minimum size cutoffs for biopsy

in an effort, even if imperfect, to reduce the risk of overdiagnosis of small cancers and biopsy of indeterminate lesions that will lead to more surgery and morbidity. Important precursors to all of the above-mentioned systems were publications by Bonavita et al.,[17] which analyzed patterns associated with benign thyroid nodules and coined the term "spongiform," and by Moon et al.,[18] which retrospectively reviewed the US images of 849 nodules with tissue diagnoses to identify US features associated with malignancy. The Kwak study[1] assembled individual features into a system whereby risk could be assigned according to the sum of these features.

The tremendous body of recently published literature focusing on independent ultrasound features contains very heterogeneous data that, despite its usefulness, suffers from limitations. These include analysis only of incidentally discovered, biopsied, or sometimes surgically excised nodules, introducing selection bias and loss of data on cytologically indeterminate nodules. Additional limitations include inter- and intra-observer variability in US interpretation, variations in US training and expertise, inconsistent definitions and weight of each sonographic criterion, and differing rates of cancer in these studies' populations. None of the studies can analyze all permutations and combinations of features, nor can they account for all relevant clinical features such as risk factors for thyroid cancer, rate of growth of thyroid nodules, and location of nodules within the thyroid gland. Rare cancer subtypes, such as Hürthle cell and medullary carcinomas, are under-characterized due to low prevalence but must not be forgotten in consideration of differential diagnoses. The risk stratification systems that have evolved all struggle most with the sonographically "indeterminate" nodules: those that have neither clearly benign patterns nor combinations of features that are clearly high-risk. Point-based systems also suffer from the assignment of point values to certain sonographic features that are not reflective of actual relative risk (i.e., three points in ACR TI-RADS do not equal three times the relative risk of one point). More recent attempts to compare the performance of these various US-based thyroid cancer risk estimation systems[19,20] have further identified that cancer detection and unnecessary biopsy rates vary according to size cutoffs as well as population malignancy rates. In the future, understanding the relative strengths and weaknesses of sonographic cancer risk estimation systems will ideally lay the foundation for a unified algorithm.

RELEVANT ADDITIONAL STUDIES

Not surprisingly, efforts have continued to define the ideal risk stratification system for predicting thyroid malignancy and recommending a biopsy. Additional techniques, such as color Doppler sonography,[21] shear wave elastography,[22] and contrast-enhanced US,[23] have been studied but not yet found to consistently add value to thyroid nodule cancer risk stratification, nor have been they been incorporated into any major model. Artificial intelligence (AI)–based computer-aided diagnosis (CAD) systems are beginning to be introduced to enhance the accuracy and consistency of interpretation of US features.[24] Meanwhile, of more immediate promise is the collaboration of an International Thyroid Nodule Ultrasound Working Group (ITNUWG) that is currently developing a universal lexicon and risk stratification system that seeks to reconcile, improve, and unify current systems.[25]

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Chapter 2

Cytology

Review by William G. Albergotti and Emad Al Haj Ali

Landmark Paper

THE BETHESDA SYSTEM FOR REPORTING THYROID CYTOPATHOLOGY

Cibas ES, Ali SZ. *Thyroid.* 2009;19(11):1159–65. doi:10.1089/thy.2009.0274

RESEARCH QUESTION/OBJECTIVES

Thyroid nodules are frequently identified either during a physical examination or, more commonly, incidentally by imaging modalities. The prevalence of thyroid nodules identified by imaging in the general population has been shown to be as high as 68%, with an increasing prevalence with age.[1] Their identification leads to a challenge in classifying and treating nodules with a risk of malignancy (ROM), while also not overtreating benign thyroid nodules, which account for 85–90% of all thyroid nodules.[2] Fine needle aspiration biopsy (FNA) plays an important role in stratifying the ROM of thyroid nodules. FNA can help avoid unnecessary surgery in patients with benign thyroid nodules, while also guiding appropriate surgery for those nodules that are potentially malignant. Historically, interpretation of thyroid FNA results was difficult, with different terminology reported by different laboratories, which limited both the interpretation of individual results and the sharing of data between institutions, which was identified as a significant problem.[3,4] Therefore, there was a need to develop a cytology classification system to better stratify the different types of cytological findings yielded by FNA. In 2007 the National Cancer Institute (NCI) organized the NCI Thyroid Fine Needle Aspiration State of the Science Conference, which ultimately led to the creation of the Bethesda System for Reporting Thyroid Cytopathology (BSRTC).

The primary aim of this landmark study was to develop a uniform but flexible reporting system for thyroid FNA cytopathology to both provide clinically relevant information to help guide patient management and "facilitate research into the epidemiology, molecular biology, pathology and diagnosis of thyroid diseases."[5]

STUDY DESIGN

This landmark paper was a consensus statement. Summary documents were developed with literature review and expert opinion subject to open review followed by an in-person conference that included pathologists, endocrinologists, surgeons, and radiologists held in October 2007 in Bethesda, Maryland, USA.

DOI: 10.1201/9781003196211-2

SAMPLE SIZE

Not applicable.

INCLUSION/EXCLUSION CRITERIA

English-language publications in PubMed dating back to 1995 with keywords determined by committee members.

INTERVENTION/TREATMENT RECEIVED

Not applicable.

RESULTS

The BSRTC was created. Six diagnostic categories were developed, which are summarized here:

- *Nondiagnostic/Unsatisfactory* (*1–4% ROM*): Every FNA should be evaluated for adequacy (presence of at least six groups of benign follicular cells, with each group composed of at least ten cells), colloid, atypia, or a specific diagnosis. A repeat aspiration is recommended for this result.
- *Benign* (*0–3% ROM*): The specimen consists of colloid and benign follicular cells; repeat ultrasound assessment in 6–18 months with repeat FNA considered if significant growth. This result occurs in 60–70% of thyroid FNAs.
- *Atypia of Undetermined Significance (AUS) or Follicular Lesion of Undetermined Significance (FLUS)* (*5–15% ROM*): Characterized by a predominance of microfollicles or predominance of Hurthle cells with scant colloid, focal features of papillary thyroid carcinoma (PTC) such as nuclear grooves, enlarged nuclei in an otherwise benign-appearing sample, small populations of follicular cells with nuclear enlargement, or an atypical lymphoid infiltrate. This result occurs in 3–6% of thyroid FNAs. Management includes repeat FNA, observation, or surgery depending on the clinical scenario.
- *Follicular Neoplasm (FN) or Suspicious for Follicular Neoplasm (SFN)* (*15–30% ROM*): This category encompasses follicular adenoma, follicular carcinoma, and hyperplastic proliferations of follicular cells. Cytology is characterized by follicular cells arranged in microfollicular or trabecular patterns, often with cellular crowding and/or large cells. Management is usually hemithyroidectomy.
- *Suspicious for Malignancy* (60–75% ROM): This category contains cells with 1–2 features of PTC or other thyroid malignancy but may be focal or sparse. Management is hemi- or total thyroidectomy.
- *Malignant* (*97–99% ROM*): Cytomorphologic features are diagnostic of malignancy; 3–7% of thyroid FNAs will have this result, and the management is thyroidectomy.

STUDY LIMITATIONS

The primary limitation of this manuscript is that it is based on a relatively low level of evidence (level 5, expert opinion). Although the statement was developed through a rigorous literature review, multiple drafts, and discussion periods, as well as in-person presentations and debates, there is inherent bias in these types of publications. Furthermore, there was no interpathologist or intrapathologist variability reported or suggestions for training of cytopathologists.

STUDY IMPACT

Given that the main purpose of its terminology is clarity of communication, the importance of the BSRTC can be appreciated in its facilitation of communication among cytopathologists, endocrinologists, surgeons, and radiologists. As a result of this high-fidelity classification system, diagnoses are made more accurately, a higher percentage of thyroid nodules that undergo surgery are for malignancy (i.e., fewer diagnostic operations), and ultimately patients receive better care. Following the 2009 publication of the BSRTC, it has been widely adopted and is considered the standard-of-care guidelines both in the United States and internationally.[6] Because of its high sensitivity and high negative predictive value (NPV), it has proven to be an effective and robust thyroid cytopathology classification system to guide the clinical management of patients with thyroid nodules.[7] Beyond the direct impact on clinical care, it has in turn spurred better research into the epidemiology, molecular biology, diagnosis, and treatment of thyroid diseases and facilitated research collaborations across institutions. However, despite its widespread adoption, there has been shown to only be 64% concordance in BSRTC classification between local cytopathologists and expert thyroid cytopathologists, with less experienced cytopathologists more commonly providing indeterminate diagnoses (55% vs. 41%), suggesting a need for further education and experience.[8]

RELEVANT ADDITIONAL STUDIES

Following the publication of the BSRTC in 2009 there has been a dramatic shift in the way indeterminate thyroid nodules are evaluated. There was widespread acknowledgement that thyroid surgery was overtreating the 70–90% of indeterminate nodules that would ultimately be diagnosed by operation as being benign. Around the same time there was increased recognition that predictable genetic alterations underly most thyroid malignancy. For instance, *BRAF*, *RAS*, and *RET/PTC* mutations are found in approximately 70% of PTC, *RAS* mutations and PAX8-PPARλ rearrangements are commonly identified in follicular thyroid carcinoma, and *RET/PTC* mutations in medullary thyroid carcinoma. It was this realization that galvanized the idea that if these predictable mutations (among many more now recognized) are not detected in indeterminate nodules, then malignancy could be more safely excluded.[9] Therefore, over the subsequent decade, molecular testing developed rapidly to improve the diagnostic accuracy as well as minimize cost and unnecessary surgery for indeterminate cases.[10]

Molecular testing – with Afirma (Veracyte, Inc., South San Francisco, CA, USA) and ThyroSeq (Sonic Healthcare USA, Rye Brook, NY, USA) being the two most prominent

and widely used examples – was commercially introduced in the early 2010s with the goal of improved risk stratification of indeterminate thyroid nodules, and especially ruling out potential malignancy in this situation (high sensitivity and NPV) and thus justify a nonsurgical, observational approach rather than a diagnostic thyroidectomy. These molecular tests were initially developed as rule-out tests but have been refined over the years with multiple iterations, most recently ThyroSeq v3.0 and Afirma GSC, which have shown improved positive predictive value (PPV) but still remain primarily used as rule-out tests with NPV rates of up to 97%.[11] As a result of these advances, molecular testing was included in the 2015 American Thyroid Association (ATA) guidelines as an option for further workup of indeterminate cytological diagnoses (AUS/FLUS and FN/SFN) and have become widely adopted for management planning, and occasionally as a reflexive test.[6,12,13]

Furthermore, in 2016 a nomenclature change was proposed for encapsulated follicular variant of PTC to noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP), based on observations that this entity had a very low malignant potential.[14] Thus, based on these two significant changes in the diagnosis of thyroid malignancy, as well as an additional 8 years of data, a 2017 update to BSRTC was undertaken.[15]

Each of the six diagnostic categories remained the same, with changes including updated ROM estimates based on additional years of data, as well as the inclusion or exclusion of NIFTP as a malignancy. For instance, the ROM for AUS/FLUS is noted to be 10–30% (as compared with 5–15% in the 2009 publication); however, the authors note that a large percentage of this risk is due to NIFTPs, which if considered benign, would lower the ROM to 6–18%. The higher ROM estimate, however, may be more clinically useful as that number defines the lesions that are felt to be best surgically managed. On the other hand, the ROM may be overstated due to selection bias of surgically treated lesions with a higher ROM, such as concerning ultrasound features, abnormal molecular features, or larger tumor size. Within the FN/SFN category, cytological features observed that could be consistent with NIFTP or follicular variant of PTC (such as a predominance of microfollicles or focal nuclear changes) are now included in this category: A sub-note may be offered by the cytopathologist suggesting that these two entities do remain in the differential diagnosis. The updated 2017 BSRTC also offers a "usual management" option for AUS/FLUS and FN/SFN with molecular testing.

Since the 2009 publication of BSRTC, the classification of thyroid nodule FNA cytology has grown more nuanced and more consistent. Nearly every work in this field can trace its origins back to this expert opinion–based landmark paper, which has facilitated consistent reporting, more tailored management, and advanced research on the classification of thyroid nodules.

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Chapter 3

Molecular Diagnostics

Review by Todd McMullen

Landmark Paper

INTEGRATED GENOMIC CHARACTERIZATION OF PAPILLARY THYROID CARCINOMA

Cancer Genome Atlas Research Network. *Cell.* 2014;159(3):676–690. doi: 10.1016/j.cell.2014.09.050

RESEARCH QUESTION/OBJECTIVES

Papillary thyroid cancer (PTC), the most prevalent cancer derived from the follicular cells of the thyroid, is a disease with a pathological preponderance for lymphatic spread. For many individuals, a diagnosis of PTC will not engender a poor outcome; however, predicting those patients at risk of more aggressive disease requiring more invasive surgical or medical therapy has been a challenge to physicians for more than 50 years.[1] The American Joint Commission on Cancer (TNM) system of cancer classification, first developed in the late 1960s, reflects attempts to classify cancers and provide common syntax and definitions.[2] These clinicopathologic descriptions were anchored for thyroid carcinoma by variables such as tumor size and patient age.[2] However, patients with similar demographic features and cancer presentations often will have dramatically different responses to therapy and dissimilar outcomes.[1,3] The landmark paper outlined here, "Integrated Genomic Characterization of Papillary Thyroid Cancer," (*Cell* 2014),[4] sought to identify the dominant role and nature of the driving somatic genetic alterations in PTC. This effort was part of The Cancer Genome Atlas (TCGA) genomics program that has since examined over 20,000 primary cancer and matched normal specimens spanning dozens of cancer types. The goal was to classify this common thyroid neoplasm into molecular subtypes that better reflect the underlying properties of differentiation that drive its response to therapy and determine patient outcomes.

STUDY DESIGN

This was a multiplatform analysis of 496 cases of PTC (324 classic type, 99 follicular variant, 35 tall cell, and 9 uncommon variants) designed to represent the most common thyroid carcinoma seen clinically worldwide and excluding poorly differentiated or dedifferentiated specimens. These cancer specimens with matched germline DNA from blood or normal thyroid tissue were submitted for whole exome DNA sequencing, RNA sequencing, microRNA (miRNA) sequencing, single-nucleotide polymorphism (SNP) arrays, DNA methylation arrays, and reverse-phase protein arrays. The data, publicly

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curated and available for future work (https://portal.gdc.cancer.gov/), was designed to identify somatic mutations, which included single-nucleotide variance, insertions and deletions, fusions, and copy number alterations, with a goal of identifying driver mutation events as well as characterizing the gene expression signatures associated with those mutations. This genotypic information was then correlated with clinical and pathological measures of differentiation and patient outcomes. Of the 496 primary malignancies sampled, 390 were analyzed on all the major platforms. Cancer purity and patient age, gender, MACIS score, and clinical outcome data were assessed and compared against the driver mutations identified and overall gene expression signatures. The investigators then defined subsets of molecular subgroups of functionally related genes and developed classification schemes sorted by cellular phenotypes. A thyroid differentiation score (TDS) across the entire cohort was defined by phenotypic markers, including production of thyroglobulin, thyroid peroxidase, and 14 other markers of iodine metabolism and thyroid hormone production.

SAMPLE SIZE

In total, 496 cases of PTC (324 classic type, 99 follicular variant, 35 tall cell, and 9 uncommon variants) designed to represent the most common thyroid carcinoma seen clinically worldwide.

INCLUSION/EXCLUSION CRITERIA

Poorly differentiated and undifferentiated cancers were excluded from this study in order to better study signaling, differentiation, and drivers of malignancy in the "quiet" PTC genome.

INTERVENTION OR TREATMENT RECEIVED

Not applicable

RESULTS

In this compendium the authors identified oncogenic drivers (somatic single-nucleotide variants/insertions/deletions, gene fusions, or somatic copy number alterations) in 96.5% (388/402) of cases with informative DNA exome sequence data, a substantial advance relative to the prior literature. They identified new oncogenic drivers such as EIF1AX, which encodes a protein involved in protein translation, and PPM1D, and CHEK2, which encodes proteins involved in DNA repair. The multiplatform analysis revealed that oncogenic driver mutations were associated with different thyroid cancer clinical, pathological, and differentiation characteristics. The most common driver mutations, *BRAF* and *RAS*, were defined by classic subtype and follicular variant histological patterns, respectively. Follicular variant histology was also associated with perturbations in *PTEN*, *PPARG*, and *TSHR* genes. The number and density of mutations in this cohort correlated highly with age, as well as risk of recurrence, as outlined in the 2009 American Thyroid Association (ATA) guidelines and the traditional clinical

risk stratification system for differentiated thyroid cancer, the MACIS score. The work confirmed prior signaling studies indicating the critical role of MAPK pathway signaling in PTC. The genetic analysis also identified TERT promoter mutations in less well-differentiated PTC tumors, and these mutations were not associated with *BRAF* gene mutations. Of note, unlike some other endocrine tumors, viral drivers of oncogenesis were not identified in PTC.

The authors postulated that the relatively low overall density of somatic mutations in PTC, compared to other cancer types, may explain the underlying mechanism for the generally indolent clinical behavior of this carcinoma type. The authors also provided conclusive evidence that the driving mutations are typically clonal events and that differences in driver mutations can lead to profound and important changes in genomics signatures and signaling such that some cancers may signal exclusively through MAPK (i.e., *BRAF*) while others signal through both MAPK and the PI3K pathways (i.e., *RAS*). To explore signaling and differentiation, a 71-gene signature was derived from 391 samples with exome and RNA sequencing data from *BRAF*^{V600E} and *RAS*-mutated tumors to show how gene profiling from each tumor resembled *BRAF*^{V600E} or *RAS*-mutant profiles, and a *BRAF*^{V600E}-*RAS* (BRS) score was calculated. All *BRAF* mutations other than *BRAF*^{V600E}, PAX8/PPARG fusions, and 4/6 EIF1AX were *RAS*-like, whereas BRAF fusions and RET fusions were *BRAF*^{V600E}-like. Lastly, a thyroid differentiation score (TDS) based on 16 thyroid metabolism and functional genes was calculated, which was highly correlated with global changes in gene expression that could be correlated with tumor grade, risk, and MACIS score. TDS and BRS were highly correlated, though independently derived, validating their use and suggesting these scores reflect similar biological behavior determined by the gene expression of PTC.

Cluster analysis was undertaken on four genomic datasets and identified two meta-clusters with *BRAF*^{V600E} and *RAS*-like profiles, which were further divided into distinct subtypes based on messenger RNA (mRNA) and miRNA expression and DNA methylation. These subtypes differed in terms of gene mutations, histology, and risk profiles, e.g., one cluster in the *BRAF*^{V600E}-like meta-cluster contained most of the tall-cell variant PTCs.

miRNA (which functions in posttranscriptional regulation of gene expression) was also examined and showed that overexpression of miRNA 21/204 and loss of expression of miRNA 204 correlated with a more aggressive phenotype.

The author's overarching conclusion was a proposed reclassification of PTC to reflect these genetic drivers and thus stratify tumors based on corrupted downstream signaling pathways.

STUDY LIMITATIONS

The prognostic value of the genetic signatures identified relies on accurate clinical annotation. Ideally, this would include detailed historical variables collected over long time periods, as well as details related to treatment responses. However, the TCGA

project was not designed for detailed annotations of patient outcomes, and the clinical follow-up was relatively short.[5] The extensive volume of data is also challenging to analyze and requires a priori knowledge of gene function that may not represent, in magnitude or nature, the role of individual genes in the context of different tumors and their unique gene expression signatures.[6] The choice to exclude follicular thyroid and Hurthle cell carcinoma cases from this analysis deprives the study of an opportunity to highlight other important unique genetic drivers. Lastly, high-dimensional single-cell technologies will likely extend the work of the TCGA project to provide increased resolution for clinically relevant gene expression signatures.[7]

STUDY IMPACT

At the time of publication of this landmark paper, the application of surgery and radioactive iodine for PTC was guided by clinical and pathological characteristics that included tumor size, patient age, and the extent of lymphatic spread.[1,2] Molecular markers in thyroid cancer guidelines were neither dissuaded nor recommended, and National Cancer Comprehensive Network (NCCN) and ATA guidelines did not recommend or address genetic markers in terms of prognostic value or differentiation.[1,8] In the past 8 years, TCGA genomic assessments are moving into the mainstream as both diagnostic and the prognostic management tools for thyroid carcinoma. Multiple studies now demonstrate how genomic studies can add value to the more traditional clinical pathological systems used to prognosticate for PTC, and it is predicted that molecular genetic analysis will be a requirement in future thyroid cancer treatment guidelines.[9–11]

RELEVANT ADDITIONAL STUDIES

In 2014 genetic markers for oncogenic transformation were considered most valuable in assessment of indeterminate nodules. The Afirma System (Veracyte, San Francisco, CA), followed by ThyroSeq (Sonic Healthcare, Rye Brook, NY) and ThyGenX (Interpace Diagnostics, Parsippany, NJ), were commercially available tests introduced around the time of the publication of this landmark paper.[12,13] While *BRAF* and *RAS* mutations featured prominently in the application of these preoperative tests, many of the other gene elements identified in the TCGA paper were not yet applied or analyzed in commercial tools. Since their introduction nearly a decade ago, there remains significant discussion regarding patient selection and the diagnostic utility of fine needle aspiration (FNA) accuracy.[13] This continues to drive efforts to understand genomic drivers of PTC, and the integrated genomics approach to PTC by the TCGA has been cited by the literature nearly 1,000 times. It is the comparative backbone of many studies examining genetic signatures of PTC and other variants of thyroid cancer. For example, Kasaian et al. in 2015 examined the genomic and transcriptomic landscape for anaplastic thyroid cancer, using the Cancer Genome Atlas study as a comparator to identify changes in the molecular profile as tumors progress through different stages of differentiation.[14] Thus the TCGA data has been a stepping-stone for understanding not only PTC but other follicular cancer variants, including poorly differentiated carcinoma, as well as pediatric and other thyroid cancer patient subgroups.[15,16]

The parameters guiding the adjuvant treatment of thyroid cancer have also been strongly influenced by careful study of the genetic underpinnings of PTC. Risk stratification is a key component of the management of thyroid carcinoma and has traditionally relied heavily on the TNM criteria. However, an updated classification of thyroid cancers based on differentiation, or mapping tumor signatures associated with *BRAF* or *RAS* mutations, will help to classify these tumors with greater precision and better inform the selection of adjuvant therapy.[17] Development of novel targeted therapies also continues to rely on the TCGA database for validating targets and understanding changes in signaling pathways with respect to different driver mutations.[17–19]

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Chapter 4

Ablation

Review by Hannah Nieto and Neil Sharma

Landmark Paper

US-GUIDED PERCUTANEOUS RADIOFREQUENCY VERSUS MICROWAVE ABLATION FOR BENIGN THYROID NODULES: A PROSPECTIVE MULTICENTER STUDY

Cheng Z, Che Y, Yu S, Wang S, Teng D, Xu H, Li J, Sun D, Han Z, Liang P. *Sci Rep.* 2017;7:9554. https://doi.org/10.1038/s41598-017-09930-7

RESEARCH QUESTION/OBJECTIVES

Thyroid nodules are common; even in palpably normal thyroids, the prevalence of nodular disease is up to 60%, with over 90% being benign[1] – the majority of these require no treatment. However, some nodules cause compressive symptoms, while others are of cosmetic concern and need intervention. Minimally invasive techniques (radiofrequency ablation [RFA], microwave ablation [MWA], laser ablation [(LA], and ethanol ablation [EA], as well as high-frequency ultrasound [HIFU]) have gained popularity in recent years. Users report ease of use, with good effectiveness and safety compared to surgical options, and they can be performed in an outpatient setting. While EA is mostly used for cystic nodules,[2] RFA, MWA, LA, and HIFU are applied to solid/predominantly solid nodules with volume reduction ratios of 80–90% reported at 1 year after treatment; however, many studies are retrospective and do not directly compare techniques, and so there is uncertainty as to which approach is most efficacious.[2–4] While more recent studies have further answered this question,[5,6] this landmark paper was the first to prospectively compare RFA and MWA in terms of efficacy and safety to provide a benchmark for further studies in these emerging techniques.

STUDY DESIGN

This was a prospective nonrandomized multicenter study carried out between 2013 and 2015 from eight centers in China.

SAMPLE SIZE

A total of 1,252 patients were studied, with 649 patients undergoing RFA for treatment of 687 benign thyroid nodules and 603 patients undergoing MWA for treatment of 664 benign thyroid nodules.

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INCLUSION/EXCLUSION CRITERIA

Benign thyroid nodules were included (malignant or follicular lesions were excluded), and these had to be proven benign by either two fine needle aspirate cytology samples or one histopathological core needle biopsy. In terms of nodule characteristics, the maximal diameter was not smaller than 2 cm, with progressive growth and a solid component that was greater than 20%. For study inclusion, patients also had to be symptomatic (such as neck pain, foreign body sensation, compressive symptoms) and have cosmetic concerns or hyperthyroidism from an autonomously functioning nodule, with no prior treatment given. Patients with severe symptoms, malignancy, or suspicion of malignancy; or those who had undergone a prior thyroid operation or who taking medication for their thyroid; or had a documented contralateral vocal cord palsy were excluded from the study population.

INTERVENTION OR TREATMENT RECEIVED

The study intervention was RFA (VIVA RF generator, STARmed, Goyang South Korea) with an 18-gauge, internally cooled RFA electrode, with a control of MWA (KY-2000 2450 MHz microwave system, KY-2000, Kangyou Medical, Nanjing, China) using a 16-gauge Teflon-coated internal-cooled microwave antenna. Both were specifically designed for use in thyroid nodules.

One ablation session was performed per nodule, with the patient in a supine position on continuous monitoring (blood pressure, oxygen saturations, pulse rate, and electrocardiogram [ECG]). Sterile technique was followed with 1% lidocaine used as local anesthetic. Target nodules were identified with real-time ultrasound (US). Cystic components were aspirated prior to ablation. The electrode/antenna was introduced into the nodule under US guidance and 20–50 W applied for MWA and 25–60 W for RFA. For both techniques hydrodissection was used for cases where the ablated nodule was situated at the upper or lower poles or near nerves/viscera. This is standard practice to reduce the risk of thermal injury to these structures.[7,8] The patient's voice was monitored during the procedure, and patients were observed for 30 minutes after the procedure.

The RFA and MWA techniques were compared by evaluating nodular maximal diameter reduction ratio, nodular volume reduction ratio, and the incidence of complications. Vascular (proportion of vascularized nodule measured by color Doppler flow), symptomatic (10-cm visual analogue score, patient self-measured), and cosmetic scores (physician measured) preprocedure and at 3, 6, and 12 months follow-up during the first year and at 6 to 12 months thereafter were also measured.

RESULTS

In terms of maximal diameter reduction rate, both techniques significantly reduced the nodule diameter, but the reduction was significantly higher with RFA than with MWA at 6 months, 12 months, and last follow-up, but not at 3 months. Similarly, the volume reduction ratio was significant for each treatment individually, but was significantly better in the RFA group compared to the MWA group at 6 months (84.1% vs 78.4%), 12 months (89.6% vs 82.5%), and at last follow-up (91.3% vs 81.1%), with no significant

difference between the two treatments at 3 months (67.6% vs 64.4). However, in terms of the patients' symptoms, there was no difference between the two treatments with regard to their mean vascular, symptomatic, or cosmetic scores. Both treatments significantly improved the clinical symptom scores at all time points.

The other important consideration in this study was the comparison of side effects and complications, and there was no significant difference in these outcomes between RFA and MWA. There was, however, a 4.78% (31/687) (RFA) and 6.63% (40/664) (MWA) major complication rate (total 71 patients), which included voice change, nodule rupture, and nerve injury. The majority of major complications were due to voice change, which had resolved in all cases within 3 months and occurred in 4.49% (29/687) in the RFA group and 5.8% (35/664) in the MWA group. One patient in the MWA group developed ptosis from a sympathetic chain injury that resolved with time. A further 2% (13/687) in the RFA group and 2.49% (12/664) in the MWA group experienced hemorrhage/hematoma. Side effects of pain requiring oral analgesia, cough, or fever were experienced by <5% patients in both groups.

STUDY LIMITATIONS

The major limitation of this study was that the patients were not randomized, as this could have affected the allocation of the patients to each treatment type. The baseline characteristics of each treatment group of patients beyond age and gender were not compared in this study, which would have been useful given the lack of randomization. The study also did not encompass surgery as an alternate treatment, which would have better reflected the clinical treatment options currently available. The study also included predominantly cystic nodules, which could have given an artificially elevated volume reduction ratio, and the current recommendation is for ethanol ablation of cystic nodules.[4] The authors did not include data on whether the two study groups were similar in terms of average cystic content of nodules, although all nodules were at least 20% solid – in keeping with current recommendations for ablation. A final important limitation of the study was the lack of long-term follow-up, with the mean follow-up duration being 13 months. Lengthier follow-up is important to determine recurrence rates as well as late complications such as hypothyroidism.

STUDY IMPACT

New outpatient-based techniques have recently become available for ablation of symptomatic benign thyroid nodules, potentially obviating the need for surgical removal of the gland. These include RFA, LA, HIFU, and MWA. Percutaneous EA is recommended for primarily cystic lesions but is not as effective for nodules that are predominantly solid.[2,9,10]

RFA is an image (US)–guided thermal ablative procedure that provides one potential alternative to surgery for symptomatic benign thyroid nodules and may be particularly suited for individuals who decline surgery or are high risk for surgical intervention. During RFA the moving shot technique is used, where the operator moves the RFA

needle within the nodule and observes the tissue changes with US that occur due to heat-induced necrosis.[11] Care must be taken laterally in the thyroid capsule to prevent heat damage to the recurrent laryngeal nerve – hydrodissection was undertaken in 35.1% (457/1351) of patients in this landmark paper to minimize the risk of this complication. Immediate nodule shrinkage is seen, with continued size reduction occurring over the next few months. The technique is most efficient for nodules with a volume that is less than 10 mL,[11] and it may be used for treatment of benign nonfunctioning nodules or benign autonomously functioning thyroid nodules (causing hyperthyroidism).

This landmark paper concludes that RFA is a suitable and safe alternative to MWA for ablation of benign thyroid nodules, with a significantly greater shrinkage of nodule volume than MWA and comparable improvement of patients' symptoms. This is in keeping with later studies and consensus statements issued since publication of this landmark paper.[8]

RELEVANT ADDITIONAL STUDIES

A more recent systematic review, published after the reviewed landmark paper, has also validated RFA as a safe method for managing benign thyroid nodules, but highlights the lack of long-term follow-up for most studies.[12] Another recent study emphasized that long-term follow-up of 2–3 years after ablation is important due to the potential for regrowth around the undertreated periphery of the nodule.[13]

A recent international consensus statement[8] outlines the application of all US-guided ablation procedures not only for benign disease, but also for cancer, and advises on appropriate case selection and management. The main obstacle limiting widespread adoption of these new technologies is access to relevant expertise to perform the procedures. While this landmark paper importantly helps prove the validity and safety of RFA and MWA, further studies are required to compare new ablative procedures with surgical management in order to better reflect current clinical practice.

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Chapter 5

Surgeon Volume

Review by Akie Watanabe and Sam M. Wiseman

Landmark Paper

IS THERE A MINIMUM NUMBER OF THYROIDECTOMIES A SURGEON SHOULD PERFORM TO OPTIMIZE PATIENT OUTCOMES?

Adam MA, Thomas S, Youngwirth L, Hyslop T, Reed S, Scheri D, Randall P, Roman SA, Sosa JA. *Ann Surg.* 2017;265(2):402–407. doi: 10.1097/SLA.0000000000001688

RESEARCH QUESTION/OBJECTIVES

Prior research has shown that high surgeon volume (HSV) contributes to better outcomes in thyroid surgery for both benign and malignant disease[1]; however, an actual threshold for characterizing HSV versus low surgeon volume (LSV) has not been well established. Decisions on categorization have ranged from calculating an average annual surgical volume, defining the total surgical volume, to using historical definitions.[1] Different studies have also separated patient volume into two to four groups with a broad range of thresholds.[2–6] Thus, despite knowing the impact of surgeon volume on treatment outcomes, the lack of consistency in defining HSV has made it difficult to apply in clinical practice, calling for a reliable method for defining critical thyroid surgical case volume thresholds. The primary aim of this study was to define an annual total thyroidectomy threshold for HSV versus LSV that reduces postoperative in-hospital complication rates, length of hospital stay, and total cost using a restricted cubic spline (RCS) model.

STUDY DESIGN

Retrospective cohort study in which data between 1998 and 2009 were collected from the United States Health Care Utilization Project National Inpatient Sample Datasets (US HCUP-NIS) consisting of hospital discharge data.

SAMPLE SIZE

A reported 16,954 patients who underwent total thyroidectomy by 4,627 surgeons.

INCLUSION/EXCLUSION CRITERIA

All adult patients undergoing total thyroidectomy for benign or malignant thyroid disease were included. Only files that provided surgeon identifiers were amenable to data

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collection, which amounted to the inclusion of hospitals located in 18 states in the United States. Patients who underwent thyroid lobectomy were excluded.

INTERVENTION OR TREATMENT RECEIVED

Annual surgeon volume was calculated as the number of total thyroidectomies performed by the surgeon per year. An RCS modal was used to determine a threshold that defined HSV versus LSV, and its impact on postoperative complications, length of hospital stay, and hospital costs were assessed. Complications were characterized by having at least one in-hospital complication, including endocrine-related (i.e., hypoparathyroidism or recurrent laryngeal nerve [RLN] injury) issues; bleeding; wound infection; respiratory, cardiac, or urological issues; in-hospital mortality; and overall complications.

RESULTS

A reported 4,627 surgeons performed a median of 7 cases per year (ranging from 1 to 157 cases). Most surgeons (51%) performed on average one case per year. The rate of having at least one in-hospital complication was 6%, with 2% being endocrine-related. By multivariate analyses, increasing average annual case volume was associated with fewer postoperative complications ($p < 0.001$). The RCS curve identified a threshold of 26 cases per year; HSV was therefore classified as performing >25 cases per year, while LSV was classified as performing ≤25 cases per year after including additional simulation analyses. A similar threshold was also obtained when using the RCS curve model on thyroid cancer patients. Patients treated by low-volume surgeons had a higher nonwhite population (30% vs. 20%, $p < 0.0001$), less insurance coverage (93% vs. 97%, $p < 0.0001$), and were more likely to be treated at nonacademic hospitals (43% vs. 18%, $p < 0.0001$). Endocrine-related (2.3% vs. 1.6%, $p = 0.01$), bleeding (1.6% vs. 1.0%, $p = 0.006$), and respiratory (1.1% vs. 0.7%, $p = 0.0002$) complication rates were higher in the LSV group. The LSV group also had a 12% longer length of hospital stay (95% confidence interval [CI] 3–21%, $p = 0.006$) but comparable hospital costs (2% increase, 95% CI –5 to 10%, $p = 0.57$). Within the LSV group, higher annual cases performed correlated with a decreased odds of complications (1 case per year: 87%, 95% CI 48–136%; 21–25 cases per year: 3%, 95% CI 1–4%).

STUDY LIMITATIONS

The main limitation of this study was its retrospective nature and its reliance on an administrative registry database. As all data collected was based on International Classification of Diseases (ICD) codes, coding and data entry errors could not be accounted for. Total thyroidectomy count was also based on procedure codes, which cannot identify errors. As data only encompassed in-hospital complications, those complications that happened after discharge were not reviewed, likely leading to an underestimation. Approximately 51% of surgeons in the LSV group only performed one total thyroidectomy per year, which may increase complication rates in this group. The study also did not perform a stratified analysis of surgeon volume and complication rates based on the severity of thyroid disease, which may involve higher procedural difficulty.

Many states (only 18 were included) were excluded due to the availability of surgeon identifiers, limiting the ability to capture a holistic presentation of the U.S. population. Lastly, the frequency of thyroid lobectomies performed was not included or evaluated. It is unclear whether performing lobectomies would influence surgeon experience and reduce their complication rates.

STUDY IMPACT

The American Thyroid Association (ATA) guidelines and previous studies have extensively outlined the role of HSV on reducing postoperative complications and length of stay in hospital; however, no study has developed a well-established method for measuring HSV. Current suggested thresholds lack consistency and quality evidence. Ultimately, this has led to limitations in clinical application. This retrospective study is the first to define a threshold of HSV versus LSV for total thyroidectomies that is mathematically calculated using a multivariate logistic regression model with RCS. RCS is a powerful tool that can be utilized to explore a dose-effect of a continuous exposure (annual surgeon volume) on an outcome (postoperative complications).[7] The model allowed the authors to determine a range of surgeon volumes that were associated with the relative log odds of having a postoperative complication while accounting for baseline characteristics, hospital status, and hospital volume. The derived threshold was 26 cases per year, from which the authors chose a threshold of 25 cases per year after including additional simulation analyses. The authors also conducted a subset analysis for thyroid cancer patients, which resulted in a similar threshold, emphasizing consistency and utility of the observations made using an RCS model. Although more studies are required to recapture similar thresholds through different population datasets using RCS, the current threshold of 25 cases per year, presented in this study, shows potential in being a clinically applicable definition of HSV versus LSV across all types of thyroid disease that undergo total thyroidectomy. Of course, surgeon volume can be highly variable depending on different countries' health systems, patient populations, and referral and practice patterns; therefore, studies should consider applying this model across each country to define what is the most accurate and appropriate threshold for their distinct populations. RCS can also be used to analyze the dose-effect of annual surgical volume on length of hospital stay as a different means of exploring HSV thresholds. Finally, this study creates an opportunity for future researchers to use RCS in defining an annual surgical volume threshold for HSV versus LSV based on the occurrence of postoperative complications during thyroid lobectomies, central/lateral neck dissections, operations performed for benign versus malignant disease, and/or parathyroidectomies.

RELEVANT ADDITIONAL STUDIES

With moderate-quality evidence, the ATA guidelines in 2016 suggested that thyroidectomies being performed by high-volume surgeons for benign disease, such as Graves' disease or toxic multinodular goiter, led to improved clinical outcomes[8]; however, the specific definition of HSV was not clearly stated.[8] The classification of surgeon volume in the literature has, in fact, been very heterogeneous. One of the older

studies in this area published by Sosa et al. in 1998 categorized patient volume into four groups (1–9, 10–29, 30–100, and >100 cases annually). They found that complication rates after total thyroidectomy were significantly lower in the highest-volume group, with the lowest-volume group having the highest complication rates (1–9 cases: 16.1% vs. >100 cases: 4.3%, $p < 0.001$). The length of hospital stay was also significantly longer in the lowest- compared to highest-volume group (1–9 cases: 2.4 vs. >100 cases: 1.6 days, $p < 0.001$).[9] This study recognized the importance of surgeon volume on thyroid surgery outcomes. Subsequent studies have reported different classifications of LSV versus HSV from dichotomized thresholds ranging from 30 to 70 cases per year[10,11] to those that created three categories such as <10 (LSV), 10–99 (intermediate surgeon volume [ISV]), and ≥ 100 cases per year (HSV).[2–6] Despite this inconsistency, most studies suggest a reduction in complication rates between HSV and LSV ranging from 2% to 16% ($p < 0.05$).[2–6,11] Classification of complications differ among studies, with most including hypocalcemia and RLN injuries.[2–5,11] Length of hospital stay has also been shown to be longer for LSV versus HSV by 0.2–0.8 days ($p < 0.001$).[9,10] Ultimately the abundance of studies confidently highlights a positive association between HSV and treatment outcomes; however, clinical application has been limited without an established definition of HSV.

The role of surgeon volume on the outcome of operations for different types of thyroid disease is important to assess. In thyroid cancer surgery, surgeon volume could be particularly crucial due to its potential effect on postoperative adjuvant radioactive iodine treatment, cancer, and survival-specific outcomes; however, the paucity of evidence available limits appropriate clinical guidance on this topic. The ATA Guidelines for Thyroid Nodules and Differentiated Thyroid Cancer in 2015 recommended patients with advanced disease be treated by high-volume surgeons, but did not specify a threshold.[12] Kim et al. (2018) conducted one of the largest studies in thyroid cancer patients (N = 1,103) which reported 12.3% higher disease-free survival ($p = 0.015$) and 8.9% lower positive resection margins ($p < 0.001$) among HSV compared to LSV.[13] HSV can also lower complication rates by 11.4% ($p < 0.001$).[5] These positive outcomes necessitate defining a reliable threshold for HSV that is specific for thyroid cancer patients.

Total thyroidectomies performed by high-volume surgeons can lower postoperative complication rates and length of hospital stay; however, there has been no consensus on the definition of HSV for clinical application. The selected landmark paper used an RCS model to define an HSV threshold of >25 cases per year, where its impact on treatment outcomes corroborated those in past studies. Application of this threshold in prospective studies investigating the effect of surgeon volume on thyroidectomy patient outcomes may assist with its future clinical validation and uptake.

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Chapter 6

Recurrent Laryngeal Nerve Monitoring

Review by Marika D. Russell, Rick Schneider, Che-Wei Wu, Amr H. Abdelhamid Ahmed, and Gregory W. Randolph

Landmark Paper

INTERNATIONAL NEURAL MONITORING STUDY GROUP GUIDELINE 2018: PART I: STAGING BILATERAL THYROID SURGERY WITH MONITORING LOSS OF SIGNAL

Schneider R, Randolph GW, Dionigi G, Wu C-W, Barczynski M, Chiang F-Y, Al-Quaryshi Z, Angelos P, Brauckhoff K, Cernea CR, Chaplin J, Cheetham J, et al. *Laryngoscope*. 2018;128(Suppl 3):S1–S17. doi: 10.1002/lary.27359

INTERNATIONAL NEUROMONITORING STUDY GROUP GUIDELINES 2018: PART II: OPTIMAL RECURRENT LARYNGEAL NERVE MANAGEMENT FOR INVASIVE THYROID CANCER—INCORPORATION OF SURGICAL, LARYNGEAL, AND NEURAL ELECTROPHYSIOLOGIC DATA

Wu C-W, Dionigi G, Barczynski M, Chiang F-Y, Dralle H, Schneider R, Al-Quaryshi Z, Angelos P, Brauckhoff K, Brooks JA, Cernea CR, Chaplin. *Laryngoscope*. 2018;128(Suppl 3):S18–S27. doi: 10.1002/lary.27360

RESEARCH QUESTION/OBJECTIVES

Thyroid surgery ranks among the most frequent surgical interventions. Recurrent laryngeal nerve (RLN) injury during thyroid operations and the subsequent vocal cord paresis or paralysis is a serious complication. RLN injury is a leading cause of surgical malpractice claims in the United States and Germany.[1,2]

Visual identification and the electrophysiologic characterization of the RLN via intraoperative nerve monitoring (IONM) helps to reduce the frequency of RLN injury. In a recent review of 17,688 thyroidectomies that were submitted by 112 hospitals to the National Surgical Quality Improvement Program (NSQIP) Thyroidectomy database, Schweitzer and Wiseman reported that the rate of RLN injury was 6.1% overall, with a statistically significant lower rate of RLN injury with IONM use versus no IONM use (5.7% vs 6.8%, $p = 0.003$).[3] A study from the UK found that the rate of RLN injury was 4.9% in 42,341 thyroidectomies, and IONM use reduced the risk of RLN palsy ($p < 0.001$).[4]

However, other studies did not detect a statistically significant difference between IONM versus no IONM utilization.[5] A reason for that might be the infrequent RLN

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injury rate, which adds a layer of complexity in establishing the benefits of IONM. Dralle et al. predicted the need for 9.4 million RLNs at risk per comparison arm to detect a statistically significant difference in IONM use over visual identification alone for patients diagnosed with benign multinodular goiter and 39,907 per arm for thyroid malignancy cases. The benefit could be established with a relatively smaller sample size if the surgeons had fewer years of experience and for low-volume surgeons, as their RLN injury rate is higher.[6]

In 2018, the International Neural Monitoring Study Group (INMSG) published a comprehensive two-part set of guidelines for IONM in thyroid and parathyroid surgery.[7,8] Part I addresses standards of use related to loss of nerve monitoring signal (LOS) and staging of contralateral surgery; Part II addresses optimal management of RLN invasion by cancer. This monograph was developed with the purpose of creating evidence-based guidelines to communicate standards of use, promote successful application of IONM, and enhance surgical outcomes. Given that this guideline is presented in two parts, for the purposes of this chapter, they are considered a single landmark paper.

STUDY DESIGN

The INMSG is an international multidisciplinary group composed of surgeons (otolaryngology-head and neck, endocrine, general, and oncology), laryngologists, voice and laryngeal electromyography (EMG) specialists, and anesthesiologists with expertise in neuromonitored thyroid and parathyroid surgery. An expert author panel assembled by the INMSG performed a comprehensive review of the worldwide neuromonitoring literature; review findings were synthesized with the significant clinical expertise of the author panel to generate state-of-the-art guidelines for directing IONM use during thyroid and parathyroid operations.

SAMPLE SIZE

Not applicable.

INCLUSION/EXCLUSION CRITERIA

Part I was developed with the objective of providing evidence-based definitions of fundamental concepts of IONM, including adverse EMG events and their implications for surgical strategy, especially staging of planned bilateral surgery in case of loss of IONM signal. Part II was developed with the objective of providing a framework for intraoperative decision-making for the management of the RLN invaded by thyroid cancer based on preoperative glottic function, intraoperative surgical information, and dynamic real-time neuromonitoring data. These guidelines were developed with the intent to promote accurate and uniform application of IONM in order to enhance quality of care in thyroid and parathyroid surgery.

INTERVENTION OR TREATMENT RECEIVED

Not applicable.

RESULTS

Building on initial guidelines published by the INMSG,[9] Part I outlines the clinically significant applications of IONM, including neural electrical mapping and dissection of the RLN, identification of anatomic variants, and intraoperative prediction of impending neuropraxia and prognostication of neural function after lobectomy. The document also communicates standards of IONM use related to equipment setup and troubleshooting, highlighting potential equipment challenges associated with prognostic testing errors (where LOS is considered a positive test for postoperative vocal cord paralysis [VCP]). Normative EMG data for the vagus nerve, RLN, and external branch of the superior laryngeal nerve (EBSLN), along with evidence-based standard definitions of adverse EMG events occurring during surgery, are also presented. These evidence-based electrophysiologic "signposts," including initial recommended baseline EMG amplitude, EMG findings associated with impending neuropraxia, LOS, and intraoperative recovery of EMG signal, are presented as a "roadmap" for surgery. A primary feature of the document is the recommendation for incorporating neuromonitoring data into the surgical strategy by staging total thyroidectomy if LOS was documented into an initial hemithyroidectomy, followed by a planned later completion surgery. A secondary and related recommendation is for the surgeon to forego concerns about the impact of altering the surgical plan and instead place the patient's best interests at the center of surgical strategy. Finally, a suggested postoperative management strategy for completion thyroidectomy in the setting of postoperative VCP is presented.

Part II outlines recommended surgical strategies for management of the RLN invaded by malignancy. Management strategies are depicted in various algorithms, which assimilate several different types of information and laryngeal/oncological risk-benefit factors, including preoperative clinical and laryngeal examination (whether normal or revealing ipsilateral or contralateral VCP) and radiological findings, intraoperative surgical information (including the nature and extent of neural involvement and possibility of complete resection), and EMG data (including the ability to proximally stimulate a nerve associated with preoperative VCP). Individual patient- and disease-related factors such as age, expectations regarding voice change and aspiration symptoms, patient preference, disease aggressivity, and anticipated effectiveness of adjuvant therapy inform surgical decisions at various time points. These algorithms are presented as pathways for navigating perioperative patient counseling and education, as well as the difficult intraoperative decision-making often associated with surgical management of the invaded nerve.

STUDY LIMITATIONS

These guidelines were generated based on current evidence and the collective experience of the expert author panel; as knowledge continues to evolve and technological innovations occur, updates to these guidelines will be needed. Additionally, it should be emphasized that surgical skills and sound anatomic knowledge remain prerequisite to successful surgical outcomes and cannot be supplanted by IONM utilization.

STUDY IMPACT

This comprehensive set of guidelines establishes evidence-based standards of use and provides a practical framework for uniform, safe, and successful application of IONM. The information and recommendations put forth in this publication represent state-of-the-art best practice for neuromonitoring and surgical management of the RLN. Building on a substantial body of electrophysiological research, Part I uniquely provides the surgeon with an evidence-based guide for navigating dynamic EMG changes during thyroid and parathyroid surgery. A central feature of this compendium is the description of EMG changes that predict impending neuropraxia. Prompt recognition of these changes offers the surgeon an opportunity to cease or modify unfavorable surgical maneuvers, facilitating *prevention* of neurological compromise. Furthermore, should LOS occur, the surgeon is encouraged to identify the site and likely mechanism of injury through retrograde stimulation, an exercise that offers a significant learning opportunity. Undoubtedly, these guidelines represent powerful and transformative tools for enhancing surgical technique, supporting surgical education, and improving clinical outcomes.

Importantly, the recommendation for incorporation of neuromonitoring data into surgical strategy by staging of contralateral surgery when LOS occurs is highly significant. As carefully detailed in these landmark papers, staging of contralateral surgery prevents the morbidity of bilateral VCP. Furthermore, by strongly encouraging staging of surgery in the setting of LOS, this recommendation supports and validates an otherwise difficult and fraught decision the surgeon must make intraoperatively. It is a crucial and sobering reminder that the patient's best interests must always remain at the center of surgical decision-making. Imparting this recommendation during preoperative discussion with the patient supports shared decision-making and patient awareness of staged surgery as legitimate and informed by best practice guidelines.

The algorithms for management of the invaded nerve presented in Part II similarly facilitate decision-making for a highly complex and challenging task through a blend of expert opinion and evidence-based decision support. This framework promotes uniform and optimal application of IONM, facilitating implementation of best surgical practice at all levels of clinical expertise. That these algorithms are structured based on preoperative glottic function reinforces the importance of preoperative laryngeal examination, highlighting its fundamental role in guiding surgical decision-making. Additionally, this framework incorporates multidisciplinary decision-making, reinforcing its importance in provision of high-quality surgical care.

While it is anticipated that optimal application of IONM should enhance clinical outcomes, efforts to assess the impact of IONM use on rates of RLN paralysis have been hindered by a lack of standardization across studies. Importantly, adherence to the standards put forth in these guidelines is intended to reduce variability in the application of IONM, thereby facilitating communication and research efforts related to RLN management. Standardization across studies, including application of a standard definition of LOS, appropriate and timely management of equipment-associated errors, and routine employment of preoperative and postoperative laryngeal evaluation,

promises to elevate the quality of research efforts addressing IONM and surgical management of the RLN.

RELEVANT ADDITIONAL STUDIES

In 2011, the INMSG published initial guidelines establishing standards for fundamental applications of IONM, including equipment setup and use.[9] This document serves as the foundation and conceptual basis upon which the clinically oriented 2018 guidelines were developed. The 2011 guideline established standards of equipment use, including proper placement of the endotracheal tube/surface electrodes, anesthesia considerations, and algorithms for troubleshooting equipment-associated errors. Standards of waveform assessment were defined; a standard definition of LOS was first proposed by the INMSG in this publication. Standardized functional assessment of the RLN through stimulation of the vagus nerve was also proposed.

The surgical strategies outlined in the 2018 guidelines are built upon a substantial body of accumulated electrophysiological and clinical research relating to the IONM. Five key studies provide important insight into the sequential evolution of EMG changes leading to loss of neural function and underly the surgical workflow presented for management of LOS. In the first, Schneider et al.[10] conducted a retrospective analysis of electrophysiological and clinical data, detailing EMG changes observed in 52 patients with continuous intraoperative nerve monitoring (CIONM). Adverse changes associated with specific surgical maneuvers were catalogued; multiple combined events (characterized by a decrease in amplitude >50% and concordant increase in latency >10%) were found to be positively correlated with LOS and postoperative VCP. These adverse changes were reversible in 70% of subjects if the causative surgical maneuver was modified. Subsequently Phelan et al.[11] prospectively studied EMG changes with CIONM in 102 patients and refined adverse event parameters, noting improved accuracy of severe combined events (SCEs; amplitude decrease >70% and concordant latency increase >10%) for predicting postoperative VCP, with a positive predictive value (PPV) of 33% and a negative predictive value (NPV) of 97%. LOS was associated with a PPV of 83% and NPV of 98%. Modification of the surgical approach reversed EMG changes in 73% of SCEs but only 17% of LOS. The third[12] and fourth[13] studies are prospective multicenter investigations of the INMSG. In the third,[12] encompassing 21 hospitals from 13 countries, the study evaluated patients with documented persistent intraoperative LOS. Risk factors for RLN injury were identified and vocal cord function was assessed early postoperatively and at 6 months after definitive intraoperative signal loss without intraoperative recovery. When definitive, LOS was found to strongly correlate with postoperative VCP, affecting 82% of all 115 patients with persistent LOS. Segmental LOS (type 1) was associated with more severe nerve damage than global LOS (type 2). Both LOS types were found to be primarily associated with traction injury and were noted to be unaffected by variant neck anatomy in expert hands and were unresponsive to steroids. The fourth study[13] aimed to evaluate early postoperative vocal cord function in relation to intraoperative amplitude recovery and determine optimal thresholds of intraoperative amplitude recovery heralding normal postoperative vocal cord function. In 68 patients with transient RLN injury during thyroid surgery performed with

CIONM, it was determined that when nerve amplitude recovers to ≥50% of baseline after either segmental LOS (type 1) or global LOS (type 2), it is appropriate to continue surgery on the contralateral side during the same operation. The fifth study was an international registry prospective study coordinated by the INMSG, with the aim of studying RLN surgical anatomic variability and to correlate it with EMG responses.[14] The study reported 1,000 RLNs at risk from 17 centers in 12 countries and reported that a higher-than-expected amount (23%) of the RLNs had an abnormal trajectory. LOS was reported in only 3.5% of the studied RLNs; however, LOS was found to occur more frequently in patients who had an abnormal RLN trajectory, fixed or entrapped RLNs, and invasive carcinomas. Traction injury was the most common form of RLN injury (63%) leading to LOS.

Building on these landmark 2018 INMSG guidelines,[7,8] the INMSG has recently published two consensus statements on IONM training[15] and patient informed consent.[16] The first article outlines the essential elements and key recommendations for IONM training courses,[15] and the second article outlines considerations and recommended criteria to assist the processes of informed consent and shared decision-making between surgeons and patients before thyroid surgery.[16] IONM can be implemented optimally with these new guidelines and consensus statements, ultimately benefiting all thyroid surgery patients.

The 2018 INSMG guidelines represent landmark papers because they provide state-of-the-art best practice for IONM in thyroid surgery. The construction of these documents represents a significant achievement in advancing surgical care and research efforts related to IONM and management of the RLN.

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CHAPTER 7

Superior Laryngeal Nerve Management

Review by Thomas D. Milner and Eitan Prisman

Landmark Paper

IS THE IDENTIFICATION OF THE EXTERNAL BRANCH OF THE SUPERIOR LARYNGEAL NERVE MANDATORY IN THYROID OPERATION? RESULTS OF A PROSPECTIVE RANDOMIZED STUDY

Bellantone R, Boscherini M, Lombardi CP, Bossola M, Rubino F, Crea D de, Alesina P, Traini E, Cozza T, D'Alatri L. *Surgery*. 2001;130(6):1055–1059. doi: 10.1067/msy.2001.118375

RESEARCH QUESTION/OBJECTIVES

The external branch of the superior laryngeal nerve (EBSLN) is at risk of injury during thyroidectomy, primarily during dissection of the superior pole vessels. EBSLN injury results in impaired movement of the cricothyroid muscle, with a consequent reduced ability to produce higher-pitch speech and an alteration in voice fundamental frequency. Although these changes may be subtle, they can significantly affect quality of life in singers or individuals who professionally use their voice.[1] In order to aid in anatomical identification of the nerve intraoperatively, various classification systems have been developed. These include the Cernea classification,[2] which describes the relationship of the EBSLN to the superior pole vessels; the Selvan classification,[3] whereby the EBSLN's location is described with respect to the cricoid cartilage and superior pole vessels; and the Friedman classification,[4] whereby the EBSLN relationship with the inferior pharyngeal constrictor is described. Despite these classification systems, there remains controversy as to whether the EBSLN requires routine identification intraoperatively[5–8] during thyroid surgery. Current surgical techniques for EBSLN management either aim to identify the nerve (visually or with electrical neural stimulation) or make no attempt to identify the nerve, but ligate the branches of the superior thyroid vessels as distal and close to the thyroid capsule as possible. This landmark study represents the first randomized controlled trial that attempted to address this question, with the aim of determining the risk of EBSLN injury either following intraoperative visual EBSLN identification by the operating surgeon or without nerve identification.

STUDY DESIGN

Prospective randomized controlled trial conducted in the Catholic University of the Sacred Heart of Rome between January 1998 and June 2000.

DOI: 10.1201/9781003196211-7

SAMPLE SIZE

Two hundred and eighty-nine patients were included who underwent either thyroid lobectomy or total thyroidectomy, representing 459 upper thyroid pole dissections.

INCLUSION/EXCLUSION CRITERIA

All patients scheduled to undergo thyroid operations were considered for inclusion, with the operations performed by two experienced endocrine surgeons. Exclusion criteria included previous neck irradiation, previous laryngeal or thyroid operation, or any other anterior cervical operation.

INTERVENTION OR TREATMENT RECEIVED

Patients were randomly assigned to one of two groups: Group A underwent routine identification of the EBSLN through routine nerve visualization by the operating surgeon prior to dividing the superior thyroid vessels, whereas Group B underwent ligation of the superior pole vessels as distally and close to the thyroid capsule as possible, without attempting to identify the EBSLN. The patients underwent phoniatric evaluation preoperatively, on the second postoperative day, and at 1 and 6 months postoperatively. Phoniatric evaluation was performed by a single blinded assessor and included videostrobolaryngoscopy assessing for vocal cord bowing, glottic rotation, inferior displacement of the vocal cord and asymmetry of the mucosal wave, spectrographic speech evaluation, and qualitative voice evaluation according to the Yanagihara dysphonia classification.[9] The primary outcome was the incidence of EBSLN injury, while the secondary outcomes included operative time, the incidence of other complications, and length of hospital stay.

RESULTS

The two groups studied were well matched with regard to their age, sex, type of operation, thyroid pathology, and weight. None of the patients in either study cohort demonstrated either videostrobolaryngoscopic or spectrographic evidence of EBSLN injury. Three patients (one in Group A and two in Group B) described subjective feelings of phonasthenia with decreased pitch range, without any objective evidence on phoniatric evaluation. These symptoms resolved after 1–2.5 months, and while they could represent a mild, transient EBSLN injury, they had similar incidence rates between groups. Seven patients (three in Group A and four in Group B) suffered unilateral recurrent laryngeal nerve palsy following surgery, and it was not possible to assess whether they also had a concurrent EBSLN injury. Operative time was significantly longer in Group A in comparison to Group B for both lobectomies (53.3 minutes vs. 48.7 minutes, $p = 0.004$) and total thyroidectomies (98.2 minutes vs. 94.3 minutes, $p = 0.009$). The rates of recurrent laryngeal nerve injury (2.2% vs. 2.6%), transient hypocalcemia (6.6% vs. 7.2%), permanent hypocalcemia (2.2% vs. 2.6%), operative hemorrhage (0.7% vs. 0.6%), and postoperative hospital stay (3.4 days vs. 3.5 days) were similar between Groups A and B, respectively, with these all representing a nonsignificant difference.

STUDY LIMITATIONS

One of the main limitations of this landmark paper is that it is a single-institution experience, with operations only performed by two high-volume thyroid surgeons. It is therefore difficult to determine the generalizability of the results. Another principal article limitation was their means of assessment of EBSLN injury. EBSLN evaluation has proven to be challenging, with the literature lacking a universal consensus for defining injury. Several subsequent studies have advocated the use of laryngeal electroneuromyography (LEMG) to assess postoperative EBSLN function.[10] Indeed, when laryngoscopy and voice analysis alone were used to assess EBSLN function, palsy rates ranged from 0% to 6%. In contrast, with LEMG utilization, postoperative palsy rates have been reported to be as high as 58%.[11] Finally, the proportion of patients with Cernea type 1 nerves was much higher in this study (58.6%) in comparison to the literature.[10] Cernea type 1 nerves cross the superior pole vessels >1 cm superior to the upper edge of the superior pole of the thyroid lobe, in contrast with Cernea type 2A nerves, which cross the superior pole vessels <1 cm but not below the upper edge of the superior pole of the thyroid lobe, and Cernea type 2B nerves, where the EBSLN crosses the anterior surface of the thyroid superior pole below its upper edge. Cernea type 1 EBSLN anatomy is associated with a lower risk of injury, and this may have affected the EBSLN palsy rates observed in this study.

STUDY IMPACT

This study represented the first double-blinded (patient and phoniatrician) randomized controlled trial aiming to prospectively establish the optimal surgical technique for EBSLN management. It found that the rates of impaired EBSLN function were comparable following thyroidectomy performed with attempts to visually identify the EBSLN versus thyroidectomy with careful distal superior pole vessel ligation but without attempts to identify the nerve. In addition, intraoperative EBSLN exploration was associated with a prolonged operative time. This suggests that in expert hands, routine EBSLN identification is not necessary and may result in longer operative times, which has potential cost and service delivery implications.

RELEVANT ADDITIONAL STUDIES

This landmark paper demonstrated that distal ligation of superior thyroid vessels in close proximity to the gland is a safe method of protecting the EBSLN. This is supported by Lekacos et al. who recorded no cases of EBSLN injury following 227 procedures performed with low superior pole vessel ligation.[6] However, several reports have highlighted the challenge of assessing patients using videostrobolaryngoscopy and/or phoniatrics, as utilized in these two studies, and have advocated for the use of transcutaneous LEMG when assessing the EBSLN postoperatively.[2,7,12] LEMG involves the placement of a needle transducer through the skin into the cricothyroid muscle to record EBSLN output.[10] While clinical assessment may miss some occult EBSLN injuries, LEMG is likely associated with false-positive results due to incorrect needle transducer positioning. Furthermore, the identification of an occult EBSLN injury is really only of value in the research setting.

Since this landmark paper was published, there has been growing support for the use of intraoperative nerve monitoring (IONM) during thyroid operations. Stimulation of a functioning EBSLN with a 1–2 mA current using a neural probe will result in cricothyroid contraction in 100% of cases, and a detectable electromyography (EMG) waveform (using an endotracheal tube with surface EMG electrodes) in 80% of cases.[10] Therefore, this aids the surgeon with both nerve identification and confirmation of function upon completion of the procedure. IONM has the potential to be particularly advantageous for preservation of Friedman type 3 EBSLNs, as in this category the nerve passes deep to the cricopharyngeus muscle and will therefore not be visible without dissecting this muscle. Two large systematic reviews have confirmed the utility of IONM for the identification of the EBSLN, describing a nerve identification rate of 95.9% in the IONM group in comparison to 76.6% in the non-IONM group, and a significant improvement when evaluated by meta-analysis (risk ratio [RR] 0.72, 95% confidence interval [CI] 0.36–1.08, $p < 0.0001$).[13,14] These improved EBSLN identification rates also appear to translate into a reduced rate of postoperative voice handicap.[8,15–17] Lifante et al. evaluated 47 patients either undergoing IONM (n = 22) versus no monitoring (n = 25), identifying a worse 3-month voice handicap index score when IONM was not used. Masuoka et al. and Uludag et al. both utilized a specific voice questionnaire, the EBSLN Voice Impairment Index-5, identifying an improved outcome in female patients,[16] or all patients,[17] undergoing IONM. Finally, Barczyński et al., following a prospective trial of 517 patients undergoing thyroidectomy, identified a higher temporary functional voice impairment in patients undergoing visual EBSLN identification in comparison to the use of IONM.[8]

In conclusion, in their landmark paper Bellantone et al. highlight a safe technique for the avoidance of injury to the EBSLN through the meticulous dissection of superior pole vessels.[5] While this study supports this approach, it is imperative that surgeons are aware of their own practice outcomes. Thyroid surgeons should consider the use of IONM, which has been shown in a growing body of evidence in the literature to allow for improvement of both EBSLN detection and postoperative voice outcomes.

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Chapter 8

Vessel Sealing Devices

Review by Matthew Cherko and Ram Moorthy

Landmark Paper

ULTRASONICALLY ACTIVATED SHEARS IN THYROIDECTOMIES: A RANDOMIZED TRIAL

Voutilainen PE, Haglund CH. *Ann Surg.* 2000;231(3):322–328.
doi: 10.1097/00000658-200003000-00004

RESEARCH QUESTION/OBJECTIVES

A variety of energy-based devices have been introduced into surgical practice to enhance tissue dissection and hemostasis. Electrothermal vessel sealing systems apply an electric current across a blood vessel wall, generating heat, which denatures the collagen and elastin in the vessel wall, thereby sealing it. An alternative technology relies on ultrasonically generated frictional heat energy to seal vessels. Ultrasonically activated devices, including shears (UAS), were first popularized for laparoscopic surgery and have been found to be beneficial with regard to both hemostasis and operating time.[1,2] Furthermore, UAS collateral thermal injury has been shown to be approximately half that caused by bipolar systems in a porcine model.[3]

The primary aim of the landmark paper was to determine if the clinical and economic benefits of using UAS for thyroid surgery compared to conventional surgical technique, as demonstrated in an earlier matched-pair study, could be replicated in a randomized controlled trial (RCT). A secondary study aim was to determine the amount of bias due to an imbalance in the surgical experience between the two groups.

STUDY DESIGN

Patients who were to undergo total thyroidectomy or lobectomy between August 1997 and January 1999 were randomly assigned, utilizing envelopes produced via a random number table, to a UAS group or conventional surgical technique group. Separate envelopes were used for consultant endocrine surgeon and senior residents, and randomization blocks were used to ensure there were balanced treatment groups.

 DOI: 10.1201/9781003196211-8

SAMPLE SIZE

Thirty-six patients were recruited based on a sample size calculation to determine whether there would be a 40-minute time saving in the UAS group (an underestimate of the advantage seen in the earlier study) with a *p*-value of 0.05 and power of 80%.

INCLUSION/EXCLUSION CRITERIA

Surgical indications of toxic goiter, suspicion of differentiated thyroid carcinoma, or follicular adenoma were included. Patients with suspected extrathyroidal invasion by thyroid carcinoma or those who had previous thyroid (or other anterior cervical) operations were excluded. Patients with unexpected findings by frozen section pathology were also excluded.

INTERVENTION OR TREATMENT RECEIVED

Thyroidectomy was carried out in accordance with a standardized protocol and sequence. In the UAS group, thyroidectomy was performed using the harmonic scalpel (UltraCision, Inc., Smithfield, Rhode Island, USA).[4,5] The superior thyroid polar vessels were divided in the same place that they would have been if ligatures were being used in the conventional group. The UAS was used to divide the isthmus but was not used in close proximity to the recurrent laryngeal nerve (RLN) or parathyroid glands. In the conventional group, most thyroid vessels were ligated with sutures. The use of clips was limited to the tissue to be removed. Monopolar diathermy was permitted in both groups.

The primary outcome measure was operating time, with additional outcomes being intraoperative bleeding, postoperative bleeding, injury to the parathyroid glands (measured by the ratio of postoperative serum calcium level on day one compared to preoperative level), and postoperative RLN palsy (determined by indirect laryngoscopy performed by an external otolaryngologist). Time for frozen section pathology or lymph node dissection was not included in the operating time. The necessity for calcium or vitamin D supplementation and the length of hospital stay were also recorded.

RESULTS

Seventeen patients were operated on in the conventional group and 19 in the UAS group. Three patients (one in the conventional group and two in the UAS group) were excluded from analysis based on a change to the intended operative plan, and no relevant outcome measures could be obtained. Also, one patient in the UAS arm was analyzed as an intention to treat.

After covariance analysis, adjusting for the type of operation and surgeon experience between the two groups, the average operating time was significantly lower ($p = 0.024$) in the UAS group (101.5 minutes) compared to the conventional group (132.1 minutes).

This equated to a 23.2% reduction in operating time (30.6 minutes). There was no significant difference in mean volume of intraoperative bleeding when comparing the UAS and conventional groups (128 ± 122.5 mL vs. 268 ± 378.7 mL; $p = 0.16$). The mean postoperative drainage recorded in the UAS group (67.2 ± 54.0 mL) was significantly less ($p = 0.036$) than in the UAS group (51.8 ± 40.9 mL).

There was no significant difference in postoperative serum calcium level when comparing the UAS and conventional groups. (86.9% ± 9.2 vs. 88.4% ± 6.5, $p = 0.60$). Two patients in the UAS group had transient RLN palsy, which had resolved when re-examined at 6 months postoperatively. One of the conventional-group patients had a permanent RLN palsy. The frequency of permanent RLN palsy per lobectomy in the study was therefore 1.8% (95% confidence interval [CI] 0.04–9.7). The median hospital stay was comparable, at 2.5 days in the UAS group versus 3.0 days in the conventional group ($p = 0.41$). A cost/benefit analysis performed by the authors – taking into account the purchase costs, consumables, and savings in surgical time – concluded that by using the UAS in thyroidectomies, an average of $10 would be saved per operation.

STUDY LIMITATIONS

The study was adequately powered to measure a statistically significant reduction in operating time with UAS. However, the sample size was too small to distinguish the possibly more subtle differences in surgical complications, especially as only one permanent RLN palsy case and one long-term hypocalcemia case were observed. The lack of long-term follow-up data, particularly with regard to the patients with postoperative hypocalcemia, makes drawing valid conclusions regarding differences in long-term complication risk between the two approaches difficult.

Comparison of the two study groups was also complicated by their heterogeneity not only in the type of operation (lobectomy vs. total thyroidectomy) but also the underlying pathology (Graves' disease vs. suspected thyroid cancer). Type of operation and pathology not only influence operating time, which was investigated by a statistical analysis of variance, but also the incidence of postoperative hypocalcemia, RLN palsy, bleeding, and length of hospital stay, which wasn't accounted for. The authors considered cervical lymphadenectomy as a separate procedure, which was not factored into the calculated operation times but could have impacted the observations made regarding blood loss and other complications.

The variability in surgical experience was of more relevance – for example, one patient randomized to UAS was operated on without the UAS because of the surgeon's inexperience with the device. This calls into question whether it was fair to compare two techniques performed by a surgeon when they were still on their learning curve with UAS. The authors also highlighted the significant difference in experience and operating time with the UAS when comparing the consultant endocrine surgeon and the senior residents. The heterogeneity was also seen in the broad range of intraoperative blood loss that was reported for the two groups (20–500 mL in the UAS group vs. 20–1,400 mL in the conventional group).

STUDY IMPACT

Although many studies have compared the effect of vessel sealing devices on operative time and outcomes from thyroidectomy, this was the first paper reporting on an actual RCT. The 23.2% operative time saving was significant, and there was no significant difference noted in bleeding or other surgical complications. With the addition of an essentially cost-neutral analysis, this study supported the use of UAS as an effective means to reduce surgical time for thyroidectomy without adversely impacting safety, but also highlighted that experience with the device played a key role in maximizing its potential benefit.

RELEVANT ADDITIONAL STUDIES

Since publication of this landmark paper, there have been many more studies evaluating the use of vessel sealing devices for thyroidectomy, revealing the growing popularity and acceptance of such devices in the field. In a high-volume center, the trend toward the use of energy-based vessel sealing devices was highlighted with an increase over a 5-year period from 20.2% to 98.4% of all thyroidectomies.[6]

The findings of this landmark paper have been supported by much larger-scale studies, including a meta-analysis published in 2013 that included 4,061 cases, which reported that energized vessel sealing systems provided superior results compared to the conventional surgical technique in terms of operative time, with no detriment to safety outcomes.[7] Some studies have chosen to compare different vessel sealing devices with each other. Garras et al.[8] revealed in a meta-analysis of 35 RCTs (n = 2,856 cases) that ultrasonic coagulation using the Harmonic Scalpel was superior to the use of Ligasure (Medtronic, Dublin, Ireland UK) (an electrothermal bipolar vessel sealing device) and the conventional clamp-and-tie method in terms of operative time, blood loss, and risk of postoperative hypoparathyroidism. However, importantly, the reverse was true of RLN palsy rates, which were highest in the Harmonic Scalpel group. Furthermore, other case series have not shown a difference between the use of the Ligasure and Harmonic Scalpel for thyroidectomy with regard to the rate of nerve injury, bleeding, incision drainage, operative time, and postoperative calcium level.[9]

It is important to consider the further innovation in thyroid surgery that has been facilitated by the utilization of energy-based sealing devices. Minimally invasive video-assisted thyroid surgery (MiVAT),[10] robotic thyroidectomy,[11] and more recently, transoral endoscopic thyroidectomy vestibular approach (TOETVA)[12] all rely on the use of vessel sealing devices. The use of such devices for conventional-approach thyroidectomy has allowed thyroid surgeons to develop the necessary instrument handling and dissection technique that translates into the use of this technology for novel alternative approaches.

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Chapter 9

Parathyroid Autofluorescence

Review by Paulina Kuczma, Marco Demarchi, and Frederic Triponez

Landmark Paper

NEAR-INFRARED AUTOFLUORESCENCE FOR THE DETECTION OF PARATHYROID GLANDS

Paras C, Keller M, White L, Phay J, Mahadevan-Jansen A. *J Biomed Opt.* 2011;16(6):067012. doi: 10.1117/1.3583571

RESEARCH QUESTION/OBJECTIVES

The intraoperative detection of the parathyroid glands during parathyroidectomy and thyroidectomy remains a major challenge in endocrine surgery. The parathyroid glands can be difficult to identify because of their small size, resemblance to the surrounding tissue, and variable location. The accidental removal or devascularization of the parathyroid glands can lead to hypoparathyroidism with lifelong sequela, if permanent. Current preoperative localization techniques such as ultrasound, sestamibi scintigraphy, CT scans, and choline PET/CT generally detect only abnormal glands. Consequently, their intraoperative detection has relied on visual inspection by the surgeon. The goal of this study was to assess whether near-infrared autofluorescence (NIRAF) could be used to intraoperatively discriminate parathyroid glands from other tissues in the neck.

STUDY DESIGN

The authors of this pilot study compared fluorescence spectra produced upon excitation of different neck tissues with 785-nm light in patients undergoing thyroid and/or parathyroid surgery at the Vanderbilt University Medical Center.

SAMPLE SIZE

A total of 21 patients who underwent thyroid and/or parathyroid surgery.

INCLUSION/EXCLUSION CRITERIA

All patients with primary thyroid or parathyroid pathology aged 18–99 years were included.

INTERVENTION OR TREATMENT RECEIVED

Following neck exploration, different tissues were illuminated with a 785-nm laser that delivered 80 mW at the surface in vivo with a spot size of 400 µm. Fluorescence spectra

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from 800 nm to 1,000 nm from the thyroid, parathyroid, fat, muscle, and lymph nodes were acquired with a fiber optic spectrometer, processed on a laptop, and compared. In each case, the attending surgeon inspected the investigated area visually and determined the tissue type. If a tissue was excised during the surgery, the spectra were also correlated with histological findings.

RESULTS

In all patients, when the parathyroid glands were stimulated by near-infrared light at the 785-nm wavelength, they emitted bright light with peak emission at about 820 nm. Weaker autofluorescence of the thyroid was also observed, while other examined tissues (muscle, fat, or trachea) emitted no autofluorescence. Parathyroid NIRAF was 2–11 times brighter than that of the thyroid (p-value = 0.0000235). In four patients, both parathyroid and thyroid histology were available, and the results were consistent with the surgeon's visual identification of the tissues. Seven patients presented with primary hyperparathyroidism and 14 with thyroid disease and normal parathyroid glands. Both normal and hyperfunctioning parathyroid tissue produced strong autofluorescence with a constant peak emission wavelength.

STUDY LIMITATIONS

The main limitation of this study was the small number of included patients. It remains unclear if the results could have been affected by patient and disease characteristics, as the description of the cohort was incomplete. Furthermore, the study did not report how many parathyroid glands were identified per patient. Another study limitation was that, for most of the tissues evaluated, the tissue type was only determined visually by the attending surgeon. The accuracy of such subjective evaluation is highly dependent on a surgeon's experience. Although the study was performed at an expert endocrine surgery center, it is unclear how many different surgeons performed the evaluations. If the surgeon had low confidence in the identification of the parathyroid gland (which in itself is subjective), the tissue was excluded from the study, which could have contributed to a selection bias. The subjective evaluation process together with the incomplete histological validation may have led to false-positive and/or false-negative results.

STUDY IMPACT

The incidence of inadvertent parathyroidectomy ranges from 8% to 19% in patients undergoing total thyroidectomy.[1] Patients with permanent postoperative hypoparathyroidism have a higher risk of long-term morbidity and increased mortality rates.[2] In patients with hyperfunctioning parathyroid tissue, it is crucial to identify and adequately remove the diseased parathyroid glands, as persistent hyperparathyroidism requires reoperation. This landmark study introduced NIRAF as a new noninvasive tool for rapid identification of parathyroid tissue in vivo, in real time, and with high accuracy. Until then, the only methods available for intraoperative parathyroid gland identification were frozen section obtained from a biopsy or parathyroid aspiration and dosage of parathormone in the aspiration, which are both invasive and time consuming,

with a non-negligible risk of irreversibly injuring the parathyroid gland. NIRAF requires no contrast agent, so the risk of toxicity or allergenicity is eliminated. Furthermore, this technique can be used to identify both normal and hyperfunctioning parathyroid glands, which distinguishes it from preceding localization methods such as ultrasound or sestamibi scintigraphy, which only detect enlarged or hyperfunctioning glands, making this method even more remarkable. Therefore, it has been shown that NIRAF has the potential to help surgeons find (and preserve) the parathyroid glands during thyroidectomy, and thus reduce the risk of postoperative hypoparathyroidism. NIRAF can also be helpful for identification of hyperfunctioning parathyroid glands during parathyroidectomy by assisting surgeons with the sometimes lengthy and tedious search for parathyroid glands in patients with hyperparathyroidism.

RELEVANT ADDITIONAL STUDIES

The findings of this landmark paper were validated by a number of subsequent studies in larger patient cohorts for benign and malignant thyroid disease, as well as for diverse parathyroid pathologies, consistently showing stronger autofluorescence of the parathyroid glands compared to all the other neck tissues, regardless of the disease state.[3–5] Studies have also shown that NIRAF enhances parathyroid detection rates: In one study, 46% of glands were covered with soft tissues and not visible to the naked eye, but could be identified with NIRAF prior to their dissection.[6] It was shown that adding NIRAF imaging to the surgeon's naked-eye observation in patients undergoing total thyroidectomy improved the number of identified parathyroid glands from 2.5 to 3.7 per patient.[7]

The responsible fluorophore remains unknown, but different authors have suggested that it may depend on parathyroid cellularity, expression of calcium-sensing receptors, or the presence of pseudocolloid.[4,7] Interestingly, autofluorescence of the parathyroid glands is very stable: It resists formalin fixation and extreme temperatures.[8] It has been shown that it is detectable in parathyroid glands even after 2 years of cryopreservation.[9] The intensity of the autofluorescence signal remains unaffected by gland perfusion, and other methods have been developed to assess the vascularity and viability of the parathyroid glands (e.g., indocyanine green angiography or laser speckle contrast imaging). However, hyperfunctioning parathyroid glands show different NIRAF patterns than normally functioning glands: The NIRAF signal intensity is lower and more heterogeneous.[10]

Subsequently, NIRAF detection devices that facilitate parathyroid gland identification in an easily utilized manner in the operating room were developed, and currently there are two classes of NIRAF detection devices: Probe-based and image-based. The largest study using the probe-based device showed that parathyroid NIRAF was consistently greater than the thyroid and all surrounding tissues in 97% of glands evaluated.[5] The most commonly used probe-based device, the PTeye (Medtronic, Jacksonville, FL, USA), a system that employs a handheld fiber optic probe that can be used even in the presence of ambient operating room lights, was shown to have 96.1% accuracy for the detection of parathyroid glands.[11] Studies using the device showed that it has a positive predictive value of 93% and a negative predictive value of 100%.[12,13] This remarkable

accuracy has been confirmed in a multicenter surgeon-blinded trial.[14] The image-based devices include the Fluobeam system (Fluoptics, Grenoble, France), which consists of a camera with a near-infrared light source to illuminate the tissue. The emitted light is captured and displayed on a screen as a visual map, where bright spots correspond to parathyroid glands. Such devices require the operating room lights to be turned off (only the surgeon's headlight for the newest generation). Both the image- and probe-based devices detect parathyroid glands with high sensitivity (90.9% vs. 97%) and accuracy (84.6% vs. 92.3%).[15,16] The image-based systems provide spatial information and "mapping" of the surgical field and require no contact with tissue. On the other hand, the probe-based systems provide quantitative information and can be used with the ambient operating room lights turned on.

Whether intraoperative NIRAF detection influences parathyroid preservation and postoperative hypocalcemia was examined in several studies. These studies showed that the use of NIRAF lowers inadvertent parathyroid resection rates,[17–20] helping to preserve them in situ, and if removed, increasing the number of parathyroid glands found on the specimen that can be auto-transplanted.[21] Most studies reported that intraoperative NIRAF detection also reduces the frequency of transient postoperative hypocalcemia,[16,17,19,22,23] while others observed no statistically significant difference between the NIRAF and control groups.[18,20] Among the cited studies, the PARAFLUO multicenter randomized clinical trial, that included 241 patients who underwent thyroidectomy, showed that NIRAF imaging more than halved the incidence of transient hypocalcemia (from 21.7% to 9.1%), but had no effect on permanent hypocalcemia rates.[17] Furthermore, NIRAF imaging lowered the incidence of inadvertent parathyroidectomy from 11.7% to 2.5%, and of autotransplantation from 13.3% to 3.3%. A large study reported by Kim et al. that enrolled 542 patients undergoing total thyroidectomy with central neck lymph node dissection demonstrated a significantly lower incidence of postoperative hypoparathyroidism in the NIRAF group than in controls.[19] There was no difference in the permanent hypoparathyroidism rate between the two groups. The number of inadvertently resected parathyroid glands was significantly lower in the NIRAF group. Dip et al. showed a ten-fold decrease in the incidence of postoperative day 1 hypocalcemia in patients who underwent NIRAF-assisted thyroidectomy compared to the controls (from 11.8% to 1.2%).[23] Bellier et al. examined the number of parathyroid glands that can be saved and reimplanted with utilization of NIRAF during thyroid surgery.[21] Overall, of all the unintentionally removed parathyroid glands, about a third could be visualized and salvaged only due to NIRAF use after initial visual inspection. In contrast, DiMarco et al. reported that NIRAF examination of the surgical specimen does not help to salvage more parathyroid glands.[24] Another study compared outcomes of patients undergoing thyroidectomies performed by the same surgeon in periods before and after the introduction of NIRAF.[22] The NIRAF group exhibited a significantly lower postoperative hypocalcemia frequency (5.2%) than the pre-NIRAF group (20.9%), a higher mean number of identified parathyroids, and reduced parathyroid autotransplantation rates. A recent meta-analysis that included eight studies, reporting on 2,889 patients, concluded that the use of NIRAF led to an almost three-fold decrease in the incidence of transient hypocalcemia, from 22.4% to 7.11%, and a nearly two-fold decrease in parathyroid gland resection rates, from

14.39% to 7.65%, with no impact on permanent hypocalcemia or autotransplantation rates,[25] which is consistent with most other reports.

The current evidence on the utility of NIRAF-guided surgery for preserving the parathyroid glands and preventing hypoparathyroidism, particularly in thyroid cancer surgery, was summarized in a systematic review by Demarchi et al., which included 25 studies with a particular focus on thyroid cancer surgery.[26] Feitsma et al. reviewed the current literature on optical imaging–assisted thyroid surgery, including 38 articles on parathyroid autofluorescence.[27] In addition to the benefits already described, the authors highlighted significant discrepancies in the imaging protocols used and the need for standardization. In their review, Solórzano et al. summarized the current state of the intraoperative use of autofluorescence with an update on current technologies and recommendations and issued guidelines for optimal integration of NIRAF detection into existing thyroid and parathyroid surgery protocols.[28] New NIRAF devices are under continuous development: A prototype device called the Overlay Tissue Imaging System (OTIS) back-projects the fluorescence image directly onto the surgical field instead of a display monitor.[29]

In conclusion, as first described in the landmark paper and subsequently validated, NIRAF is a user-friendly, safe, and accurate tool that provides real-time intraoperative guidance for surgeons, helps reduce inadvertent parathyroid resection, identifies glands for autotransplantation, and may reduce the incidence of postoperative hypoparathyroidism and hypocalcemia. More research is needed to confirm its efficacy in decreasing post-thyroidectomy hypoparathyroidism, to evaluate its cost-effectiveness, to assess its advantages when used by less experienced surgeons, and to validate its utility especially when used in low-volume centers.

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Chapter 10

Remote Access Thyroidectomy

Review by Maureen D. Moore and Thomas J. Fahey

Landmark Paper

TRANSORAL ENDOSCOPIC THYROIDECTOMY VESTIBULAR APPROACH: A SERIES OF THE FIRST 60 HUMAN CASES

Anuwong A. *World J Surg.* 2016; 40(3): 491–7. doi: 10.1007/s00268-015-3320-1.
PMID: 26546193

RESEARCH QUESTION/OBJECTIVES

The current standard surgical approach for thyroid disease is a traditional open cervical thyroidectomy. This approach, however, usually results in a visible neck scar.[1] With the advent of remote access surgery, many novel surgical approaches to thyroidectomy have been developed in order to reduce the size and visibility of the neck scar, including moving the scar to other areas of the body such as the axilla, breast, or postauricular area.[2–5] Subsequently, natural orifice transluminal endoscopic surgery (NOTES) for thyroidectomy was developed and focused on two techniques: 1) sublingual approach and 2) oral vestibular approach (TOETVA).[6,7] Studies have shown the sublingual approach to have a higher complication rate, and therefore, TOETVA has been more studied with encouraging results and fewer complications.[6] The aim of this landmark paper was to describe the operative technique and details, patient-specific outcomes, and postoperative complications in the first series of 60 patients successfully treated with TOETVA.

STUDY DESIGN

Retrospective cohort study analyzing surgical outcomes data of one laparoscopic surgeon from a tertiary care unit of Police General Hospital, Faculty of Medicine, Siam University, who performed the first described TOETVA, from April 2014 to January 2015.

SAMPLE SIZE

One hundred and thirty-five thyroidectomy patients that included 60 patients who underwent TOETVA successfully without conversion to a traditional cervical approach.

 DOI: 10.1201/9781003196211-10

INCLUSION/EXCLUSION CRITERIA

Inclusion criteria comprised adult patients with a thyroid gland diameter no larger than 10 cm who had a diagnosis of:

1. Benign disease such as thyroid cyst, single-nodular goiter, or multinodular goiter
2. Follicular neoplasm
3. Graves' disease
4. Papillary thyroid microcarcinoma without evidence of metastasis

Patients who were unfit for surgery, had previous neck surgery or radiation of the neck, could not tolerate general anesthesia, and/or wore dental braces were excluded.

INTERVENTION OR TREATMENT RECEIVED

TOETVA was performed using a three-port technique through the oral vestibule of the lower lip by means of one 10-mm blunt-tip port for the laparoscope and two additional 5-mm ports for instruments. First, the 10-mm port was placed in the center of the oral vestibule of the lower lip, and CO_2 insufflation was initiated with a set insufflation pressure of 6 mmHg. Two 5-mm ports were then inserted at the junction between the incisor and the canine bilaterally under direct visualization using a 30-degree laparoscope. After creating a working space, the strap muscles were divided and retracted laterally with external sutures. The thyroid isthmus, along with the associated thyroid vessels, were then transected using an ultrasonic vessel sealing device. The recurrent laryngeal nerve (RLN) was identified at its insertion into the larynx and traced downward in the tracheoesophageal groove. The parathyroid glands were also identified and preserved. The specimen(s) were removed using an endobag through the 10-mm port. The strap muscles were reapproximated, and the oral vestibule incisions were closed. Oral antibiotics were prescribed for 7 days postoperatively.

RESULTS

During the study period, data was collected from 135 thyroidectomy patients of which 60 patients (44.44%) (57 females and 3 males, mean age 41.36% ± 12.24 years, range 19–65 years) underwent operations by TOETVA without conversion to a traditional cervical approach. With respect to thyroid disease classification, 34 (56.67%) of the patients had a single-nodule/cyst treated by hemithyroidectomy with isthmusectomy, while 22 (36.67%) patients were diagnosed with multinodular goiter and two (3.33%) patients with Graves' disease who were treated by total thyroidectomy or the Hartley-Dunhill procedure. Papillary microcarcinoma without metastatic disease was found in two (3.33%) patients for whom a total thyroidectomy with central lymph node dissection was performed. The average thyroid nodule size was 5.4 cm (range 3–10 cm). The overall median operative time was 115.5 minutes (range 75–300 minutes), with a median operative time for hemithyroidectomies of 90 minutes (range 75–180 minutes) and 135.5 minutes (range 105–300 minutes) for total thyroidectomies or Hartley-Dunhill procedures. The median

blood loss was 30 mL (range 8–130 mL). Postoperative complications occurred in six patients, which included temporary hypoparathyroidism in three patients (5%), temporary paresis of the RLN in two patients (3.33%), and a delayed neck hematoma in one patient (1.67%) treated nonoperatively. Mean hospital length of stay was 3.6 days (range 2–7 days).

STUDY LIMITATIONS

The main limitation of this study was its retrospective nature, which collected surgical outcomes on an operation performed by only one surgeon from a single institution. Furthermore, this approach required surgical skills that many thyroid surgeons, both in academic and community settings, may not have at their command. In addition to the need for an experienced thyroid surgeon with advanced laparoscopic skills, this procedure also requires trained operating room staff to perform this surgery safely and successfully, and therefore may not be applicable to all hospital settings. Additionally, this article addresses the safety and feasibility of TOETVA in a young, largely female Asian population without data pertaining to body mass index or facial structure, and therefore, the author's results may not be as applicable to other populations with differing body habitus. A fourth limitation includes lack of data regarding the management of postoperative pain. The length of stay for patients who underwent TOETVA (mean 3.6 days) is considerably longer than the length of stay for a traditional open cervical thyroidectomy, which is often an outpatient procedure or a 1-day stay. This may be explained by the desire of the authors to have a closer postoperative evaluation of each patient in order to determine the safety profile of TOETVA. Moreover, the authors failed to provide follow-up data, including a lack of formal cosmetic evaluation postoperatively and a lack of postoperative thyroid cancer–specific outcomes.

STUDY IMPACT

With the evolution of endoscopic surgical techniques, scarless thyroid surgery has been explored as an alternative approach to conventional cervical thyroidectomy. This study was the first to describe the operative technique of the innovative TOETVA approach, which overcomes the complications of other described remote access thyroidectomy techniques, such as the sublingual approach, while leaving no visible scars on the neck. TOETVA is similar to other oral vestibular approaches such as transoral video-assisted neck surgery (TOVANS)[8] and endoscopic thyroidectomy via the oral vestibular approach (ETOVA); however, TOVANS uses a gasless technique,[8] while ETOVA uses essentially the same technique as TOETVA. It is also the first report of the initial experience in Asia with thyroidectomy by TOETVA with a focus on technicalities, feasibility, and surgical outcomes. Since its publication, many countries, including the United States and France, have introduced this technique and published their outcomes using the TOETVA approach for selected patients. Since the adoption of TOETVA, broader indications for its use have been studied, including its role in the surgical management of thyroid cancer.

RELEVANT ADDITIONAL STUDIES

With continued use of the TOETVA approach, Anuwong et al. published their series of 200 patients who underwent TOETVA that was performed by three surgeons at their

institution. The authors were again able to show that this technique was safe and feasible with minimal pain and few complications in an expanded dataset.[1] The adoption in the United States was first reported by Udelsman et al. with their published series on the use of TOETVA in both thyroid and parathyroid surgery for seven consecutive patients.[9] Despite the small number of patients, their series reported no cases of RLN injury or hypoparathyroidism, with shorter length of stay compared to the reports published from Asia.[1,9] With respect to clinical data, the median operative time was noted to be higher than the traditional cervical thyroidectomy, with a median of 152 minutes, compared to that of 105.5 minutes for conventional thyroidectomy.[10] Additionally, in a systemic review and meta-analyses, the transient RLN injury risk was noted to be comparable to that standard cervical approach (4% vs. 3.3%, respectively). It is important to mention that studies have confirmed the feasibility of intraoperative nerve monitoring (IONM) during the TOETVA approach.[10] For example, Wang et al. demonstrated use of IONM during TOETVA in ten cases where electromyography (EMG) responses were recorded accurately without occurrence of transient or permanent RLN palsy.[11] Moreover, a large series comparing TOETVA to open thyroidectomy noted a higher rate of transient hypoparathyroidism with use of TOETVA, (10.6% vs. 9.3%); however, the difference was not statistically significant.[12] TOETVA also appears to be safe and feasible for use in selected patients with papillary thyroid cancer. A study reported by Liu et al. compared matched papillary thyroid cancer patients with tumor sizes >1 cm and ≤3.5 cm who underwent an open thyroidectomy to those who underwent TOETVA.[13] Compared with the matched open thyroidectomy group, the papillary thyroid carcinoma group had a significantly longer operative time ($p < 0.001$), greater blood loss ($p < 0.05$), more total drainage volume ($p < 0.001$), increased surgical cost ($p < 0.05$), better cosmetic satisfaction ($p < 0.001$), lower scar self-consciousness ($p < 0.001$), and better quality of life ($p < 0.001$).[13] They observed nonsignificant differences in the number of retrieved lymph nodes and metastatic central lymph nodes; the rates that the intraoperative RLN signal weakened; and of parathyroid autotransplantation, visual analog scale scores for pain, drainage duration, postoperative hospital stay, rate of complications, and oncological completeness.[13]

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Chapter 11

Robotic Thyroidectomy

Review by Mahmoud Omar, Mohamed Aboueisha, Mohamed Shama, and Emad Kandil

Landmark Paper

DIFFERENCES IN POSTOPERATIVE OUTCOMES, FUNCTION, AND COSMESIS: OPEN VERSUS ROBOTIC THYROIDECTOMY

Lee J, Nah KY, Kim RM, Ahn YH, Soh E-Y, Chung WY. *Surg Endosc.* 2010;24:3186–3194. doi: 10.1007/s00464-010-1113-z

RESEARCH QUESTIONS/OBJECTIVES

Conventional transcervical thyroid surgery is an effective operative treatment approach for most patients diagnosed with thyroid tumors. However, the postoperative cosmetic appearance and presence of postoperative neck neuropathic pain are major concerns, especially in women.[1] Endoscopic techniques have been developed to avoid cervical scars. However, they were limited by the difficulty of the approach due to the imperfect visualization and limited ability to manipulate the surgical field, leading to a relatively small number of centers around the world practicing such techniques. In 2007, robotic thyroidectomy was first introduced in Korea.[2] The incorporation of a robot into the endoscopic approach through the axilla provided a greater visualization of the thyroid anatomy, eliminated the impact of hand tremors, and provided a greater degree of instrument movement compared to the endoscopic approach alone. The primary aim of this landmark paper was to compare the postoperative outcome, including postoperative distress and patient satisfaction of robotic-assisted thyroid surgery to conventional open thyroidectomy.

STUDY DESIGN

A prospective study was carried out enrolling patients from April 2009 to early 2010. Patients were informed about the operative techniques involved in both surgical approaches (conventional open and robotic assisted), and patients chose which surgery they desired.

SAMPLE SIZE

A total of 84 patients were enrolled in the study, 41 in the robotic group and 43 in the open group.

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INCLUSION/EXCLUSION CRITERIA

Patients diagnosed with a follicular thyroid carcinoma 4 cm or smaller in diameter or a papillary thyroid carcinoma 2 cm or smaller in diameter made up the study patient population.

Study exclusion criteria were patients with previous neck operations; age younger than 21 years or older than 65 years; prior vocal fold paralysis or a history of voice or laryngeal disease requiring therapy; a malignancy with definite extrathyroidal invasion, multiple lateral neck lymph node metastases, perinodal infiltration at a metastatic lymph node, or distant metastasis; or the cancer being located in the thyroid dorsal area (especially adjacent to the tracheoesophageal groove).

The extent of thyroid resection was determined for each patient using the American Thyroid Association 2009 guidelines. All the patients underwent pretracheal, prelaryngeal, and paraesophageal prophylactic ipsilateral central compartment lymph node dissection (CCND). All surgeries were performed by a single high-volume surgeon based on surgical techniques previously reported.[2–4] Four robotic arms were used for the operation. Three arms were inserted through an axillary incision. A dual-channel endoscope was placed on the central arm, and a harmonic curved shears and a Maryland dissector (both from Intuitive Surgical, Sunnyvale, California, USA) were placed on both lateral side arms of the scope. An EndoWrist® Prograsp forceps (Intuitive Surgical, Sunnyvale, California, USA) was then inserted through the anterior chest arm.

INTERVENTION OR TREATMENT RECEIVED

This study conducted a comprehensive assessment of the patient's postoperative outcome:

a. Operative details were compared between the two surgical approaches, including operative time, intraoperative blood loss, number of retrieved central neck lymph nodes, length of hospital stay, and postoperative complications.
b. Postoperative pain and cosmetic outcomes were evaluated. All patients were given analgesics according to the same protocol and underwent the same postoperative follow-up protocol. This included the patients grading their neck and anterior chest pain at 24 hours, 1 week, and 3 months postoperatively. Cosmetic appearance was assessed by the patient using a verbal response scale (1–5, from extremely dissatisfied to extremely satisfied) at 3 months postoperatively.
c. Voice and swallowing were subjectively assessed using the validated Voice Handicap Index 10 (VHI-10) and Swallowing Impairment Index 6 (SIS-6) scales, respectively.

RESULTS

Forty-one patients underwent a robotic-assisted thyroidectomy, and 42 patients underwent a conventional open thyroidectomy. The two groups were similar in age, gender, type of operation, and their final pathologic diagnosis. The robotic-assisted

surgery group had a significantly longer operative time than the open group with a mean of (128.6 ± 36.3 vs. 98.0 ± 22.2, $p = 0.001$) minutes for total thyroidectomy and (99.3 ± 16.8 vs. 87.0 ± 14.1, $p = 0.005$) minutes for subtotal thyroidectomy. There was no significant difference between the two groups with regard to their intraoperative or postoperative complications. Both groups had a similar length of hospital stay (2.5 ± 1.2 vs. 3.2 ± 1.8 days, $p = 0.196$). None of the patients developed severe complications (e.g., permanent recurrent laryngeal nerve (RLN) injury, permanent hypocalcemia, or tracheal injury). Mobility of the vocal cords was assessed by videostrobolaryngoscopic examination performed preoperatively, then 1 week and 3 months postoperatively. Vocal cord palsy was defined as permanent when no evidence of recovery was observed beyond 6 months.

Patient satisfaction measured 24 hours after surgery did not show any difference between the two groups, but there was a significant decline in patients experiencing hyperesthesia (or excess sensitivity) in their neck from 15 (36.6%) at 1 week to 4 (9.8%) at 3 months in the robotic thyroidectomy group, while over the same time period this decreased from 41 (95.3%) to 28 (65.1%) in the open thyroidectomy group. However, in the robotic thyroidectomy group 19 patients (46.3%) reported hyperesthesia or paresthesia of their anterior chest, though this discomfort gradually resolved, and only 8 patients (19.5%) reported minimal hyperesthesia or paresthesia of their anterior chest 3 months after surgery, compared to 1 patient in the open group at 1 week and none at 3 months.

The patients in the robotic thyroidectomy group showed greater satisfaction than those in the open group with regard to their cosmetic results from surgery ($p < 0.001$). In the robotic surgical group, 37 patients (90.2%) were satisfied or extremely satisfied, whereas only 24 patients (55.8%) in open surgical group were either satisfied or extremely satisfied with their cosmetic results at 3 months postoperatively. No patient was dissatisfied with the cosmetic appearance after surgery in the robotic surgical group. But nine patients (20.9%) in the open surgical group were dissatisfied or extremely dissatisfied with their cosmetic results. Both approaches had similar voice outcomes at 1 week and 3 months postoperatively. Swallowing assessments found that the robotic surgical group had a better outcome with a lower SIS-6 score than the open surgical group at 1 week and 3 months, with p-values of 0.001 and 0.007, respectively.

STUDY IMPACT

This study was reported by the group that pioneered robotic-assisted surgery in 2007, with multiple studies showing the validity and safety of this technique.[2–4] This was the first prospective study to examine the outcome of robotic-assisted thyroid surgery compared to a conventional open approach. This study assessed multiple outcomes, including operative details, postoperative complications, postoperative pain, and cosmetic appearance, and was the first study to assess postoperative swallowing and voice outcome using a validated questionnaire.

Their extensive review of the multiple outcomes of the two approaches has suggested the superiority of robotic thyroidectomy to the traditional open approach in terms of

swallowing and cosmetic outcomes compared with the traditional open approach. This report was followed by a significant increase in the adoption of the robotic surgical technique between 2010 and 2011.[5] Based on this landmark paper and other similar studies from the United States that followed,[6–8] the American Thyroid Association in 2016 recommended that robotic-assisted thyroidectomy be performed at high-volume centers in the United States given its steep learning curve and higher costs. The improved swallowing outcomes associated with robotic surgery have turned our attention to the role that this approach may have in minimizing the change of voice and swallowing postoperatively due to the elimination of a neck incision, and possibly related to the lateral surgical approach to the thyroid gland.[9] This study has been cited up to 71 times by different institutions around the world, where it impacted thyroid surgical practice.

STUDY LIMITATIONS

The sample size in the study was relatively small for a common operation and could have affected the outcomes examined. Also, the study is limited by the follow-up period, which was only up to 3 months, which is too short to determine both the oncological and cosmetic outcomes of both surgical approaches. Surgical scars mature slowly, so scar evaluation should be delayed until after 12 months.[10] While the study is prospective, it is nonrandomized, and it is also unclear if the differences observed for the robotic surgical group would actually have an impact on the patient's quality of life. Robotic surgery itself has multiple limitations. The study didn't examine the cost-effectiveness of robotic surgery and if the observed benefits would be worthwhile.[11] The article also did not account for the learning curve and the time the surgeon takes to master this operation. While avoiding the neck scar is important in some cultures and countries, the cost-benefit ratio may make it unappealing in others.

RELEVANT ADDITIONAL STUDIES

Although robotic transaxillary thyroidectomy has been widely used in Asia, its role still remains debatable in the Western world.[12] A report of our initial experience with the first 100 cases of robotic transaxillary thyroidectomy was published in 2012 demonstrating its feasibility for various diagnoses, including selected cases of thyroid cancer and Graves' disease.[7] A meta-analysis published by our group compared the outcomes of conventional and robotic thyroidectomy.[13] The meta-analysis, which included nine studies reporting on a total of 2,881 patients, 1,122 of whom underwent robotic thyroidectomy, established no significant difference between both groups regarding the rate of RLN injury or hypoparathyroidism.[13]

Robotic thyroidectomy was adopted by the Western world without accounting for important differences in the patient population being treated, especially related to body mass size, nodule size, and gland size.[14] Subsequently, modifications were made to account for these factors, including alteration in arm positioning to minimize the risk of brachial plexus injury, the Imperial or Modena (CEATEC, Wurmlingen, Germany) retractor systems specifically designed for the Western patients' body habitus, and careful patient selection.[14] Other modifications include surgical approaches carried

out via the chest, axilla, combined axillary bilateral breast, or bilateral axillary breast approaches.[15–18] Later, the single axillary incision alone approach was adopted.[19] This approach has also been used for management of malignancy, and neck dissection for the treatment of local lymph node disease has been performed using a transaxillary robotic approach in patients diagnosed with unilateral differentiated thyroid carcinoma with cervical lymph node metastases and no prior neck surgery.[20] Multiple studies have examined the long-term oncological outcome and showed that robotic surgery has a similar survival to the conventional approach.[21–23] Patients and surgeons should be aware that while the robotic transaxillary approach offers better cosmetic results, it has a risk of injury to the brachial plexus and skin flap,[24] and it remains an investigational surgery that is considered "off-label" in the United States. Other different approaches for robotic thyroidectomy have been reported since the introduction of the transaxillary approach, and these include the retroauricular approach using a facelift incision that is usually utilized in parotid surgeries[25] and the transoral robotic approach.[26] These other approaches offer a limited dissection relative to that provided by the transaxillary approach due to differences in access to the neck. Ultimately, the choice of robotic approach is dependent on the surgeon's experience and the case being treated, as each has its benefits and limitations.[27]

Current evidence supports robotic transaxillary thyroidectomy for the surgical management of benign and malignant disease in carefully selected patients by high-volume surgeons who work in multidisciplinary specialized centers.

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Chapter 12

Graves' Disease

Review by Rajam Raghunathan, Jacques How, Roger Tabah, and Elliot Mitmaker

Landmark Paper

OUTCOME OF GRAVES' DISEASE PATIENTS FOLLOWING ANTITHYROID DRUGS, RADIOACTIVE IODINE, OR THYROIDECTOMY AS THE FIRST-LINE TREATMENT

Liu X, Wong CKH, Chan WWL, Tang EHM, Woo YC, Lam CLK, Lang BHH. *Ann Surg.* 2021;273(6):1197–1206. doi: 10.1097/SLA.0000000000004828

RESEARCH QUESTION/OBJECTIVES

"Psychologically as well as physically hyperthyroidism can be a crippling disease."[1] Selwyn Taylor, thus describing toxic goiter in his 1979 Werner lecture, reaffirmed Osler's recommendation made 70 years earlier, that "after three months of careful treatment, if the patient is not better, the question should be considered of surgical treatment. Removal of part of the thyroid gland offers the best hope of permanent cure."[1,2] The treatment of Graves' disease is a controversial topic and has centered on first-line management with antithyroid drugs (ATDs), radioactive iodine (RAI), or thyroidectomy. Despite their significant adverse event rates, ATD and RAI are often cited as the preferred options for disease management[3,4]: RAI is recommended as the next step for patients with side effects from ATD or recurrence of hyperthyroidism after ATD by both the European Thyroid Association Guideline for Graves' Hyperthyroidism (2018) and the UK National Institute for Health and Care Excellence (NICE) guideline (2019). According to the American Association of Clinical Endocrinologists/American Thyroid Association (AACE/ATA) practice guidelines, RAI has been the therapy preferred by physicians in the United States, while ATD or surgery are the preferred treatment modalities in Europe and Japan[5]; in a 2011 international survey of endocrinologists, the preferred treatment was ATDs (53.9%) over RAI therapy (45%) and thyroidectomy (0.7%).[6] Citing concerns with high costs, operative morbidity, and complication rates, surgery is often reserved for cases that are medically refractory, involve airway compression, have concurrent hyperparathyroidism, or when malignancy is suspected.[3] The primary aim of this landmark paper was to compare the long-term outcomes, including morbidity, all-cause mortality, relapse, and healthcare costs, of Graves' disease patients undergoing first-line treatment with ATD, RAI, or thyroidectomy, whether partial or total.

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STUDY DESIGN

This was a retrospective cohort study comparing the long-term outcomes of Graves' disease patients treated over a 12-year period, between January 2006 and December 2018 in the Hong Kong Hospital Authority (HKHA) database, covering over 90% of all inpatient services in that territory. The primary measured outcomes were risks of cardiovascular disease (CVD), atrial fibrillation, psychological disease, diabetes, hypertension, and all-cause mortality following first-line Graves' disease treatment. The study also compared the risk of relapse after first-line treatment until the end of follow-up, 10-year direct cumulative healthcare costs, and any longitudinal change of comorbidity profiles as estimated by the Charlson Comorbidity Index (CCI).

SAMPLE SIZE

A total of 6,385 patients with a median follow-up of 90 months who received first-line treatment for Graves' disease were analyzed.

INCLUSION/EXCLUSION CRITERIA

Patients 18 years or older with a diagnosis of Graves' disease who received first-line treatment either with ATD, RAI, or thyroidectomy were included in the study patient population. Patients were excluded if they had no hospital treatment records, were lost to follow-up after baseline, or had a pregnancy within 12 months before the index date. Patients were stratified by the three treatment modalities: ATD, RAI, or surgery. They were permitted prior ATD for ≤12 months, then assigned to the ATD group if they had no RAI or surgery 12 months after ATD initiation; to the RAI group if they had RAI alone as treatment or less than 12 months of ATD prior to definitive RAI therapy; and to the surgery group if they underwent thyroidectomy without prior ATD or following less than 12 months of ATD therapy.

INTERVENTION OR TREATMENT RECEIVED

Among those eligible patients, 74.93% received ATD, 19.95% were treated with RAI, and 5.12% underwent total or partial thyroidectomy as first-line Graves' disease treatment; 18.04% of the surgery patients had partial thyroidectomy, while 81.96% underwent total thyroidectomy.

RESULTS

Among all three treatment groups, surgery showed significantly lower risks of all-cause mortality, CVD, atrial fibrillation, diabetes, hypertension, and psychological disease than either RAI or ATD. Risk of relapse was also lowest among patients who underwent thyroidectomy, with a higher rate of relapse for partial thyroidectomy patients (4.16%) compared to total thyroidectomy patients (2.21%). Complications in the surgery group included recurrent laryngeal nerve (RLN) paralysis (9.17%), hematoma (0.92%), hypoparathyroidism (2.75%), and hypocalcemia (30.58%) most commonly. Presumably, the hypoparathyroidism measured was permanent, while the hypocalcemia

was temporary. The CCI score, which measures change in comorbidities, had an upward trend in all treatment groups over the study period. Though initially higher compared to the other two treatment groups, the CCI score for thyroidectomy was lower after 10 years. Annual and cumulative healthcare expenses, including service utilization and medication, were relatively lower in the surgery group than the ATD and RAI groups, but were similar to the other two groups after the fifth year of treatment. RAI patients had a higher incidence of diabetes and hypertension than patients on ATD. An increased risk of all-cause mortality was observed in patients treated with two doses of RAI, which aligns with the results of two previous cohort studies, noting an association between RAI dose and higher mortality risk. While RAI is reported to increase the risk of developing or worsening ophthalmopathy, the study showed a lower risk of ophthalmopathy-related psychological disorder with RAI than with ATD treatment.

STUDY LIMITATIONS

The main limitation to the study was its retrospective approach, relying on the HKHA database, in which many variables were unavailable. Information regarding free and total T_3, total T_4, body mass index (BMI), and smoking status was only partially accounted for, introducing an important source of bias in the results: a suppressed thyroid-stimulating hormone (TSH) level could still occur in the presence of a normal T_3 or T_4 level, and high BMI or smoking could act as a confounder in the development or worsening of diabetes and cardiovascular disease. Since more severe Graves' disease is often treated with surgery because it is refractory to medical therapy, the study may not be comparing like with like. Mild Graves' disease could be more common in the ATD group, while the surgery patients could have higher rates of severe Graves' disease, which would have biased the results. The incidence of RLN injury, close to 10%, was high, with no indication by the authors as to whether this was transient or permanent.[7] The financial analysis was limited geographically and may not extrapolate to other healthcare models.

STUDY IMPACT

This study demonstrates a significant improvement in all-cause mortality, morbidity, relapse, and cost over other treatment modalities thereby supporting thyroidectomy as the first-line treatment for Graves' disease in the long term. The authors show that initial thyroidectomy has both mortality and morbidity benefits over ATD or RAI, particularly regarding cardiovascular risk and morbidity over a 10-year follow-up period. The improvement in CVD after thyroidectomy provides a compelling independent argument for preferring this approach, though the physiological mechanism that underlies it requires further elucidation. The study also demonstrates that due to its lower relapse rate, surgery has the lowest 10-year healthcare cost as a first-line treatment compared to the other treatment modalities, despite having higher up-front annual costs. This long-term cost savings could be due to the low relapse rate with surgery compared with other treatment modalities. The study reiterates an association with higher rates of diabetes post-RAI. Multiple possible mechanisms are suggested to explain this, including RAI-induced damage to pancreatic islet cells and RAI-induced hypothyroidism, leading to greater insulin resistance.[8] Additionally, ophthalmopathy-related psychological disease

induced by Graves' disease treatments and its impact on patient quality of life have also been addressed. While RAI is reported to increase the risk of developing or worsening ophthalmopathy, the authors showed a lower risk of psychological disease with RAI than with ATD. This creates an opportunity for further research into patient quality of life and experience with Graves' disease and its treatment.

RELEVANT ADDITIONAL STUDIES

A significant aspect of the study requiring further elaboration is the association between surgery for Graves' disease and the reduction in cardiovascular morbidity. Several recent studies have highlighted the connection between definitive therapy for Graves' disease and the decrease in cardiovascular morbidity and mortality. A 2019 linked-record cohort study from Wales demonstrated that excess mortality in Graves' disease was driven primarily by exposure to uncontrolled hyperthyroidism. The study showed that a survival benefit could be gained by prompt elimination of the hyperthyroid state, whether by ATDs or RAI. Regardless of treatment modality, the underlying predictor of cardiovascular morbidity and mortality in the Welsh study was the effectiveness of that treatment in rapidly eliminating hyperthyroidism and in maintaining a normal TSH.[9] Surgery was not one of the treatments considered in the Welsh study. Nevertheless, the conclusions of the Welsh study support the principal finding of this landmark paper that surgery is the most effective treatment for Graves' disease, as it most definitively and rapidly decreases hyperthyroidism.

Another study from 2020 demonstrated the cardiovascular benefits of thyroidectomy in a retrospective cohort of 164 Graves' patients at a single institution undergoing either total thyroidectomy or RAI ablation. Patients in this study who underwent total thyroidectomy had a higher rate of resolution of cardiac arrhythmia after treatment than those who underwent RAI ablation. This further supports thyroidectomy as the treatment of choice for Graves' patients with concurrent cardiovascular comorbidity.[10]

The superiority of thyroidectomy for Graves' patients with CVD was corroborated in a 2021 retrospective study of 151 Graves' patients with cardiovascular comorbidity undergoing total thyroidectomy versus medical therapy with ATD or RAI. Patients who underwent thyroidectomy compared with those who had medical therapy showed better resolution in hypertension (44.7% vs. 18%), improvement in tachyarrhythmia (85.9% vs. 66%), and amelioration of heart failure (75% vs. 50%).[11] Further studies in the literature point to the cardiac physiology that underlies thyroidectomy as superior to medical management of Graves disease. A 2013 report highlighted the ineffectiveness of ATD in completely reversing the cardiovascular manifestations of Graves' disease even after a euthyroid state was attained.[12] Another recent prospective case-control study showed a significant improvement in diastolic heart function, measured by the biomarker of myocardial damage N-terminal pro-BNP, in surgery patients compared to patients who received medical therapy with ATD.[13]

In a 2022 follow-up study to this landmark paper, a retrospective cohort analysis was carried out of relapsed or persistent hyperthyroidism cases despite medical management.

Surgery was found to have lower rates of all-cause mortality, CVD, atrial fibrillation, ophthalmopathy, psychological disease, and cancer over a 10-year follow-up period. These observations also highlight the need for further research into the incidence of cancer in Graves' disease patients who undergo surgery versus ATD or RAI.[14]

The optimal management for Graves' disease has remained a matter for considerable discussion. Current guidelines highlight the importance of shared decision-making between patients and providers when considering treatment options.[3,5,15] A 2022 review article by Cohen et al. highlights the concurrent or shared interviewing of a patient by an endocrinologist and a surgeon as an effective way of presenting patients with a more complete picture of their treatment options.[15] While surgery was the preferred management option in only 0.6% of cases based on a 2011 multinational survey of endocrinologists, 15% of patients in a shared interviewing model opted for total thyroidectomy over other treatments.[15,16] Adoption of an interdisciplinary discussion of the management of Graves' disease should be considered. The landmark paper by Liu et al. demonstrates the benefits of surgery over ATD and RAI for Graves' disease treatment when considering all-cause mortality, morbidity, CVD, relapse, and cost. Possible morbidity related to RLN palsy and permanent hypoparathyroidism is unique to the surgery group. Surgery has a higher morbidity in the first 5 years. However, the lower CCI score at 10 years compared with ATD and RAI does suggests a lower long-term morbidity in the surgery group. While multiple small randomized studies found no significant difference in quality of life (QoL) between treatment types,[17,18] a large multicenter 2019 Swedish cohort study that used thyroid-specific instruments for measuring QoL found that RAI-treated patients had worse or higher thyroid-specific (ThyPRO) QoL scores (mean score 27) than ATD patients treated for 18–21 months (mean score 21) or than surgically treated patients (mean score 22).[19] Similar findings were reported by other studies employing the SF-36 and thyroid-specific QoL questionnaires.[20–22]

The cardiovascular and metabolic consequences of Graves' disease therapy, underlying physiology, and psychological sequelae of treatment all constitute fertile ground for future investigation. Recent literature corroborates the finding that surgery is the preferred treatment for Graves' disease in patients with concurrent cardiovascular comorbidities, which show definitive improvement with surgical management. Taken together, these investigations support the case for reconsidering surgery in Graves' disease as the standard of care.

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Chapter 13

Goiter

Review by Lucinda Duncan-Were and Carla Pajak

Landmark Paper

FIVE-YEAR FOLLOW-UP OF A RANDOMIZED CLINICAL TRIAL OF TOTAL THYROIDECTOMY VERSUS DUNHILL OPERATION VERSUS BILATERAL SUBTOTAL THYROIDECTOMY FOR MULTINODULAR NONTOXIC GOITER

Barczyński M, Konturek A, Hubalewska-Dydejczyk A, Gołkowski F, Cichoń S, Nowak W. *World J Surg.* 2010;34(6):1203–1213. doi:10.1007/s00268-010-0491-7

RESEARCH QUESTION/OBJECTIVES

There has been much debate, but little evidence, on the best surgical management of nontoxic multinodular goiter (MNG). Total thyroidectomy has been thought to result in definitive treatment with the lowest risk of recurrence, but with the highest risk of morbidity from hypoparthyroidism and recurrent laryngeal nerve (RLN) palsy,[1] whereas more conservative approaches, such as subtotal thyroidectomy, have higher rates of clinically relevant recurrence but lower morbidity rates.[1] This landmark paper has assessed three techniques used for the surgical treatment of bilateral MNG, focusing on the recurrence rates and morbidity from total thyroidectomy (TT), bilateral subtotal thyroidectomy (BST), and the Dunhill operation (DO) at a 5-year interval. The primary outcome measure was prevalence of recurrent goitre with the need for redo surgery. Secondary outcomes included morbidity rates, specifically hypoparathyroidism and RLN palsy.

STUDY DESIGN

This randomized control trial (RCT) was conducted by utilizing computer-generated permuted block sequencing of patients allocated by opening sealed envelopes in the operating theater. Study participants were blinded to the operation for the duration of the trial.

SAMPLE SIZE

Six hundred patients from one center in Poland over a 3-year period (January 2000–December 2003) were allocated equally to three groups: TT, BST, and DO.

INCLUSION/EXCLUSION CRITERIA

Patients presenting for first-time thyroid surgery with bilateral nontoxic MNG, with posterior aspects of both thyroid lobes appearing normal on ultrasound, were included

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in the study. Exclusion criteria were MNG at the posterior aspect of the thyroid lobes, suspicion of thyroid cancer, previous thyroid surgery, thyroiditis, subclinical or clinically overt hypothyroidism or hyperthyroidism, pregnancy or lactation, age younger than 18 years or older than 65 years, American Society of Anesthesiologists (ASA) grade 4, and inability to comply with the follow-up protocol. All participants underwent a high-resolution Doppler ultrasound of the neck, fine needle aspiration of the thyroid, and measurement of serum free T_3, free T_4, thyroid-stimulating hormone (TSH), and serum thyroid peroxidase antibodies.

INTERVENTION OR TREATMENT RECEIVED

Random allocation placed patients into three groups: TT, DO, and BST. The DO procedure was defined as unilateral extracapsular total thyroidectomy and contralateral subtotal thyroid lobe resection (leaving a thyroid stump of approximately 2 g of normal remnant tissue). The BST procedure was defined as leaving bilateral thyroid stumps of approximately 2 g each. All operations were performed by three experienced endocrine surgeons, each performing approximately one-third (+/–2) of the operations in each of the three group. Thus, each surgeon performed an approximately equal number of procedures.

RESULTS

Recurrence was defined as a hypoechoic or hyperechoic nodular lesion within the remnant thyroid tissue that was at least 5 mm in diameter at 5-year follow-up. Recurrence was identified in 0.52% of TT, 4.71% of DO, and 11.58% of BST ($p = 0.01$ for TT vs. DO, $p = 0.202$ for DO vs. BST, and $p < 0.001$ for TT vs. BST). Redo surgery was performed in 0.52% of TT, 1.57% of DO, and 3.68% of BST ($p = 0.03$ for TT vs. BST).

Transient postoperative hypoparathyroidism was detected in 10.99% of TT, 4.23% of DO, and 2.1% of BST. Transient and permanent RLN injury rate was 5.49% and 1.05%, respectively, from TT compared to 4.23% and 0.79% from DO and 2.1% and 0.53% from BST. Thyroid cancer, permanent RLN palsy, and permanent hypoparathyroidism rates did not differ substantially between the groups.

STUDY LIMITATIONS

A few minor limitations have been identified in this study. Most MNG recurrences tend to occur 10–20 years after surgery[2]; thus it is possible that many recurrences were not captured by this study protocol. However, the study was extended to 10-year follow-up, which identified higher recurrence rates within all three groups. Study participants were also recruited from one center in southern Poland known for iodine deficiency and a high incidence of goiter, meaning primary outcomes may not be generalizable to populations from iodine-rich areas. All operations were also performed only by high-volume thyroid surgeons, which itself reduces the overall risks of postoperative complications and may limit the applicability of study findings to lower-volume surgeons. Furthermore, since study recruitment for this paper, intraoperative nerve monitoring (IONM) has become

commonly adopted to aid in the identification of the RLN, and this adjunct may further contribute to an overall reduction in nerve injuries.[3] Near-infrared autofluorescence for parathyroid identification was also not utilized in this study, but is rising in popularity among thyroid surgeons and may reduce the risk of postoperative hypoparathyroidism. Adoption of these adjuncts has the potential of making thyroid surgery even safer. Finally, intention to treat scores were not calculated, and postoperative bleeding was not recorded, even though it poses significant morbidity in the immediate postoperative period. Subgroup analyses would have been beneficial as well, but data on participant age, body mass index, surgeon use of vessel sealing devices, retrosternal MNG location, etc., was not reported. These details may have impacted the study outcomes but were not accounted for.

STUDY IMPACT

Surgery is the only definitive treatment option for the treatment of bilateral, benign MNG[4] (ATA guidelines). While this is generally accepted, there is some debate over the optimal surgical procedure, with lesser operations thought to reduce morbidity while still achieving cure. This RCT, along with another study reporting on its 10-year follow-up,[5] have demonstrated that for MNG patients, TT is the procedure of choice, as it nearly eliminates the risk of recurrence without the previously feared increase in long-term morbidity, especially when performed by experienced surgeons. This paper clearly demonstrated that leaving residual thyroid tissue exposes patients to a high risk of recurrence and that this recurrent MNG is not treatable by levothyroxine suppression. This led to a subset of patients (0% TT vs. 0.53% DO vs. 1.05% BST) requiring completion surgery to relieve clinically relevant tracheal compression. While this was not significant at 5 years of follow-up, at 10 years of follow-up there was a significant difference, with revision surgery being required in 1 (0.6%) TT versus 5 (2.8%) DO versus 14 (8.0%) BST study patients ($p < 0.001$ for TT vs. BST and $p = 0.019$ for DO vs. BST). While TT significantly decreased the risk of recurrence when compared to BST – hazard ratio (HR) 0.795 (0.643–0.982), $p < 0.001$ at 10 years (log rank test) – it is important to note that recurrences among TT may still occur, albeit at the lowest frequency for all surgical approaches, with one series reporting recurrences occurring in only 0.3% of patients when followed for 25 years.[2] This landmark paper also addressed the safety concerns of TT versus more conservative procedures. At both 5- and 10-year follow-up, there was no significant difference in the number of permanent RLN injuries (cumulative at 10 years): 1.05% and 1.1% TT versus 0.79% and 1.4% DO versus 0.53% and 1.4% BST (5 years and 10 years, respectively). There was a significant increase in transient hypoparathyroidism among patients undergoing TT in comparison to the DO versus BST (10.99% vs. 4.32% vs. 2.1%; $p < 0.001$ and $p = 0.007$, respectively). However, when considered at the 10-year follow-up, permanent postoperative hypoparathyroidism occurred in 1 (0.6%) TT versus 2 (1.1%) DO versus 5 (2.9%) BST patients (nonsignificant differences), thus reinforcing the safety of TT when carried out for treatment of MNG. In fact, the greatest risk occurred if reoperative surgery was required, as this has been shown to pose an up to 20-fold increased risk of morbidity when compared to primary surgery.[6] This strengthens the argument for up-front TT as being the safest choice of initial surgery for treatment of MNG.

RELEVANT ADDITIONAL STUDIES

The findings of this article are supported by the American Thyroid Association (ATA) guidelines on the surgical management of goiter, which clearly recommends TT as being the procedure of choice.[4] A similar trend favoring TT for disease control has been shown among patients with Graves' disease: A meta-analysis of four trials found that TT led to an overall reduced risk of recurrent hyperthyroidism.[1] Despite Graves' disease being a separate disease entity, comparable studies of surgical techniques also found an increase in only transient postoperative hypoparathyroidism. A subsequent RCT reported in 2019 evaluating patients with Graves' disease compared TT to near-total thyroidectomy (NTT) (bilateral remnants of ≤1 g) to test the underlying hypothesis that bilateral remnants may increase preservation of the upper parathyroid glands.[7] However, no significant difference in postoperative hypocalcemia was observed (19% NTT and 21% TT, $p = 0.84$). With regard to prevention of recurrence, their findings echoed observations of the selected landmark paper: TT had a high cure rate with a negligible recurrence rate, while NTT failed to reduce the risk of morbidity, including hypoparathyroidism and RLN injury.[7] Furthermore, the rate of reoperation was higher among the NTT group ($p = 0.07$), and technical difficulties prevented surgeons from preserving remnants in 4/103 patients.[7] Thus, it seems that among experienced surgeons, the perceived reduction in harm of doing less than a TT did not outweigh the actual benefits of a TT.

Finally, brief consideration should be given to unilateral disease. ATA guidelines state that if the contralateral lobe is essentially normal, a hemi-thyroidectomy (HT) may be considered,[4] again, with the underlying rationale being disease control while minimizing the risk of complications. However, a retrospective observational study of 493 patients found that HT resulted in 80% of patients requiring lifelong hormonal supplementation and had no significant reduction in RLN injuries.[8] In the same study, 11.4% of patients who underwent an HT went on to require a TT after having a carcinoma diagnosed by final histology.[8] Thus, especially in the setting of bilateral nodules, TT may be preferred to HT, especially with indeterminate preoperative cytology, or even for patients who simply wish to avoid repeat surgery.[9] In conclusion, in the hands of an experienced thyroid surgeon, up-front TT should be considered for the management of MNG.

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Chapter 14

Complications

Review by Sendhil Rajan, Muhammad Shakeel, and Sebastian Aspinall

Landmark Paper

A MULTI-INSTITUTIONAL INTERNATIONAL STUDY OF RISK FACTORS FOR HEMATOMA AFTER THYROIDECTOMY

Campbell MJ, McCoy KL, Shen WT, Carty SE, Lubitz CC, Moalem J, Nehs M, Holm T, Greenblatt DY, Press D, Feng X, Siperstein AE, Mitmaker E, et al. *Surgery.* 2013;154(6):1283–1291. doi:10.1016/j.surg.2013.06.032

RESEARCH QUESTION/OBJECTIVES

Compressive hematoma is the most feared complication of thyroidectomy, as it is unpredictable and can evolve rapidly. Postoperative hematoma can lead to airway compromise and even mortality due to increased pressure in the cervical compartment.[1] Over time, thyroidectomy has changed from an operation requiring an inpatient stay to one that is now being delivered as an outpatient day case procedure.[2] The aim of this study was to improve understanding of the timing and risk factors for postoperative hematoma to help refine patient selection for outpatient thyroidectomy. In order to safely deliver outpatient thyroidectomy, knowledge of risk factors for and timing of cervical hematoma are crucial to minimize the risk of this potentially fatal complication occurring after discharge from hospital. We selected this article on hematoma after thyroidectomy as the landmark paper because it was a multicenter study that considered the most risk factors for hematoma, as well as timing from surgery, and so provided valuable observations to help identify the patients who can safely undergo day-case thyroidectomy.

STUDY DESIGN

This was a retrospective case-control study in which data from 1997 to 2012 was collected by 55 surgeons from research/audit databases or hospital records from 15 centers in the United States, Canada, and the Netherlands. For each case, three controls who did not develop a hematoma were randomly selected from patients who underwent thyroidectomy at the same institution.

SAMPLE SIZE

Two hundred and seven patients who developed a cervical hematoma following thyroidectomy during the study period were identified.

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INCLUSION/EXCLUSION CRITERIA

The study only included patients who developed a hematoma requiring return to the operating theater. Patients were identified from pre-existing research, quality assurance programs, operative databases, and hospital financial records.

INTERVENTION OR TREATMENT RECEIVED

For each case and control, clinical, operative, and postoperative notes were reviewed, and variables were recorded on a standard worksheet. Worksheets from participating institutions were then pooled onto a spreadsheet for statistical analysis at the coordinating institutions of the University of California, San Francisco and Brigham and Women's Hospital, Boston. Continuous variables were analyzed with a student's *t* test and categorical variables with a chi-square test, as well as a generalized logistic model on multivariable analysis to predict independent risk factors for hematoma for 576/829 patients with complete information.

RESULTS

Median time from end of index thyroidectomy to return to the operating theater was 7.0 hours (interquartile range 2–10 hours). Ninety-nine out of two hundred and seven (47%) returned to the theater within 6 hours, 163/207 (79%) within 24 hours, and 185/207(89%) within 72 hours. The longest period after thyroidectomy taken to return to the theater for management of a hematoma was 9 days.

Univariate analysis showed that hematoma was more common in the elderly ($p = 0.018$), males ($p = 0.04$), smokers ($p = 0.037$), when antiplatelet/anticoagulant drugs were not withheld for surgery ($p = 0.001$), bilateral thyroidectomy ($p = 0.011$), concurrent parathyroidectomy ($p = 0.022$), higher blood loss ($p < 0.001$), use of a drain ($p < 0.001$), larger glands ($p = 0.004$), benign pathology ($p = 0.042$), lower core temperature ($p < 0.001$), and higher blood pressure ($p < 0.001$).

On multivariate analysis, use of a drain ($p < 0.001$), Graves' disease ($p = 0.011$), benign pathology ($p = 0.002$), active use of antiplatelet/anticoagulant drugs ($p = 0.026$), use of hemostatic agents ($p = 0.056$), and higher weight of specimen ($p = 0.004$) were independently associated with hematoma development. Odds ratios and confidence intervals associated with each of the independent risk factors of developing a hematoma are listed in Table 14.1.

Other factors analyzed were mean serum thyroid-stimulating hormone (TSH), Hashimoto thyroiditis, chronic obstructive pulmonary disease (COPD)/asthma, previous neck surgery, lymph node dissection, mean surgeon experience, mean operative time, use of a vessel sealing device, season of operation, perioperative steroids, and postoperative subcutaneous heparin; none of these factors showed a significant association with hematoma development on univariate analysis.

Table 14.1 Independent Variables Correlated with Increased Risk of Postoperative Cervical Hematoma on Multivariable Analysis

Risk Factor	Odds Ratio	95% Confidence Interval
Drain placement	2.79	1.68–4.65
Graves' disease	2.43	1.22–4.85
Benign pathology	2.22	1.35–3.57
Active antiplatelet or anticoagulation medication	2.12	1.10–4.13
Use of a hemostatic agent	1.97	1.21–3.18
Mass of pathology specimen	1.01	1.00–1.01

STUDY LIMITATIONS

The study was retrospective and nonrandomized. Cases were identified from a diverse range of sources, including pre-existing databases and hospital records. Controls were randomly selected from cases in participating institutions, but the method of how these were selected was not described. The full dataset was clearly not present in all cases, as only 576/829 (69.4%) were included in the multivariate analysis. Time to return to the operating theater, but not time to diagnosis of hematoma, was analyzed, which doesn't determine whether there were any delays to return to the theater, whether hematomas occurred that were managed nonoperatively, or what the time actually was from end of thyroidectomy to the diagnosis of hematoma. It wasn't recorded whether or not these bleeds occurred after discharge from the hospital. Additionally, all the patients included in this study were recruited only from tertiary referral centers. All these factors could potentially have introduced bias and impacted the study observations.

STUDY IMPACT

Although attitudes toward outpatient thyroidectomy vary across the world,[3–5] day-case surgery has substantial healthcare cost savings, with excellent reported outcomes.[4] Identification of risk factors for, and timing of, postoperative hematoma has hastened the move to outpatient thyroid surgery.[6] As post-thyroidectomy hematoma is an uncommon occurrence, single-center studies are unlikely to identify enough cases to determine risk factors in a multivariate analysis, and therefore these studies are, by necessity, retrospective.

This landmark paper was one of the first multicenter studies to examine both risk factors and timing of post-thyroidectomy hematoma. Although outpatient thyroidectomy was already established at the time this paper was published, the risk factors for bleeding identified, and the findings that most bleeds occurred >6 hours following surgery, are sanguine reminders that hematoma does not always occur in the early postoperative period and not all patients will be suitable for day-case surgery.

RELEVANT ADDITIONAL STUDIES

The year before this landmark paper was published, another excellent study by Promberger et al. from a single center in Austria reported on 30 years' experience with

thyroidectomy in an area of endemic goitre and showed that hematoma occurred in older patients, males, after greater extent of resection, and following reoperative surgery. This study found that 336/417 (80.6%) of hematomas requiring intervention occurred within 6 hours of surgery, and this group concluded that day-case surgery may be feasible in selected patients undergoing unilateral thyroidectomy.[7]

Older well-known single-center studies such as the report by Burkey et al. had found a low incidence of bleeding 42/13,817 (0.3%) following thyroidectomy, but had not identified any significant risk factors. However, only 18/42 (43%) of hematomas occurred within 6 hours of operation in this study, and bleeding was associated with higher morbidity and length of hospital stay.[8] Similarly, Leyre et al. in a single-center study of 6,830 patients from France reported that a high proportion of hematomas occurred >6 hours post-thyroidectomy and concluded that day-case thyroidectomy was not safe.[5]

The inability to reliably identify those patients most at risk of bleeding following thyroidectomy, and the occurrence of bleeding after 6 hours postoperatively in a significant proportion of patients, resulted in the British Association of Endocrine and Thyroid Surgeons (BAETS) discouraging day-case thyroidectomy in the United Kingdom[9] However, at the same time, outpatient thyroidectomy was gaining popularity in North America, with good outcomes being reported.[4] Snyder et al. reported successful outpatient thyroidectomy in 1,063/1,136 (93.6%) of planned procedures from a single center with a low overall complication rate. Hematoma only occurred in two of their patients, with neither requiring bedside decompression.[4] In 2013 the American Thyroid Association published an interdisciplinary consensus statement outlining eligibility criteria for the safe practice of outpatient thyroidectomy, which is an excellent reference document for surgeons undertaking day-case thyroid surgery.[2]

Since then, several analyses of large databases have been undertaken such as that reported by Mahoney et al. based on 11,552 thyroidectomies from the American College of Surgeons National Surgical Quality Improvement Program that identified independent risk factors for hematoma such as male sex, black race, diabetes, and bleeding disorders. Interestingly this study also found that the use of energy-based vessel sealing devices protected against hematoma.[10] Weiss et al. analyzed risk factors for hematoma in 150,012 thyroidectomies reported in the National Inpatient Sample database between 1998 to 2010 in the United States and found that male sex, black race, age, inflammatory thyroid disease, partial thyroidectomy, chronic kidney disease, and bleeding disorders increased the risk of haematoma.[6] In a multivariate analysis of 39,104 thyroidectomies from the United Kingdom Registry of Endocrine and Thyroid Surgery age, male gender, reoperative surgery, retrosternal goiter, and total thyroidectomy were found to correlate with an increased risk of reoperation for bleeding, but the low risk of bleeding following hemithyroidectomy led the authors (and subsequently BAETS) to endorse it as a day-case procedure in selected patients when undertaken by high-volume surgeons.[3] Talutis et al. analyzed 19,346 thyroid and parathyroidectomies in the Collaborative Endocrine Surgery Quality Improvement Program from the United States and found that men, longer operating time, complexity of procedure, and age were independent risk factors for hematoma.[11]

Our knowledge of the risk factors and timing of post-thyroidectomy hematoma has improved with time, and this has enabled us to better select patients who can safely undergo outpatient thyroidectomy and helped with the development of current guidelines for managing this complication.[12] This landmark paper was the first to investigate both risk factors and timing in a multicenter study and so significantly contributed to our understanding of this important subject.

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Chapter 15

Hypoparathyroidism

Review by Richard D. Bavier and David Goldenberg

Landmark Paper

LOW PARATHYROID HORMONE LEVELS AFTER THYROID SURGERY: A FEASIBLE PREDICTOR OF HYPOCALCEMIA

Lindblom P, Westerdahl J, Bergenfelz A. *Surgery.* 2002;131(5):515–520.
doi:10.1067/msy.2002.123005

RESEARCH QUESTION/OBJECTIVES

In the early 2000s, several case series had shown that thyroid surgery could be safely performed as a same-day procedure.[1–3] However, a significant barrier to widespread adoption of same-day thyroid surgery was the ability to predict which patients were at risk for developing postoperative hypocalcemia. At the time, there was no agreed-upon etiology for postoperative hypocalcemia, and prevailing theories included hemodilution[4–7] and transient hypoparathyroidism.[5,6,8,9] Without a firm understanding of its etiology, a reliable method for determining which patients were at risk for developing hypocalcemia was unobtainable. Therefore, to ensure patients did not develop symptomatic hypocalcemia following hospital discharge, a common practice was for patients to remain inpatient and be monitored with or without calcium and vitamin D supplementation until an upward trend in daily calcium levels was observed.[10–13] Initially, postoperative total serum calcium was proposed as a predictor of hypocalcemia. However, it was shown to have poor sensitivity.[6,7,13,14] Therefore, before the surgical community could fully adopt same-day total thyroidectomy, a more thorough understanding of its underlying cause, and a method of predicting which patients would develop hypocalcemia, was needed. This landmark paper aimed to investigate whether post-thyroidectomy serum levels of parathyroid hormone (PTH) could predict biochemical and symptomatic hypocalcemia.

STUDY DESIGN

A prospective cohort study at a single institution collected data from consecutive patients undergoing bilateral thyroid operations.

SAMPLE SIZE

Thirty-eight patients undergoing total or near-total thyroidectomy.

DOI: 10.1201/9781003196211-15

INCLUSION/EXCLUSION CRITERIA

All adults undergoing total thyroidectomy or near-total thyroidectomy for both benign and malignant pathology were included. Patients who underwent only unilateral surgery (thyroid lobectomy) were excluded.

INTERVENTION OR TREATMENT RECEIVED

Serum calcium and PTH levels were obtained at multiple times during the patient's perioperative course, including 1 day prior to surgery, immediately after induction of anesthesia, after the resection of the first thyroid lobe, after resection of the second thyroid lobe, on postoperative days 1–3, and at their 1-month postoperative follow-up appointment. Biochemical hypocalcemia was defined as a serum calcium concentration that was less than 2.00 mmol/L on two or more occasions postoperatively. Symptomatic hypocalcemia was assessed via a patient-reported questionnaire and a need for calcium supplementation. Mann-Whitney U and Fischer exact testing were used in the univariate analysis. Factors associated with postoperative hypocalcemia were then included in a stepwise multiple linear regression analysis.

RESULTS

Thirty-eight patients met study inclusion criteria, with 20 undergoing total thyroidectomy and 18 undergoing near-total thyroidectomy. Indications for surgery included Graves' disease (26 patients), goiter with compressive symptoms (10 patients), multinodular goiter (1 patient), and suspected papillary thyroid cancer (1 patient). Patient age ranged from 15 to 80 years (median 35 years), with a strong female predominance (32 women/6 men).

Ten of the thirty-eight patients (26%) included in the study met the criteria for biochemical hypocalcemia postoperatively. Comparing the 10 patients who developed biochemical hypocalcemia postoperatively with the 28 who did not, no difference was found with regard to age, gender, preoperative calcium level, preoperative PTH level, operative time, volume of thyroid tissue resected, and frequency of parathyroid gland autotransplantation. However, serum PTH levels after resection of the second lobe were lower among patients who developed biochemical hypocalcemia ($p < 0.001$). Furthermore, within 24 hours of surgery, three patients developed symptomatic hypocalcemia diagnosed with positive Chvostek and Trousseau signs, and all of these patients had serum PTH levels below the reference range after resection of their second thyroid lobe. In addition, 17 patients reported muscle irritability and self-administered calcium carbonate supplementation within the first 3 days postoperatively.

By univariate analysis, age, preoperative serum calcium concentration, number of parathyroid glands identified intraoperatively, operative time, and serum PTH level after surgery were associated with postoperative biochemical hypocalcemia. On multivariate linear regression analysis, an independent association was established between PTH levels after resection of the second thyroid lobe and biochemical hypocalcemia. Additionally, a PTH level below 1.6 pmol/L correctly predicted 9 out of 10 patients

who developed biochemical hypocalcemia (sensitivity 90%, specificity 75%) and 12 out of 17 patients with symptomatic hypocalcemia (sensitivity 71%, specificity 81%). Comparatively, a serum calcium level of less than 2.00 mmol/L on postoperative day 1 diagnosed 9 out of 10 patients with biochemical hypocalcemia (sensitivity 90%, specificity 82%) and 9 out of 17 patients who developed symptomatic hypocalcemia (sensitivity 52%, specificity 76%).

STUDY LIMITATIONS

The paper was limited in its scope, sample size, and surgical indication. It took place at a single institution with a relatively modest sample size. In addition, indication for surgery was homogenous and not representative of all practices – nearly 70% of the study population underwent thyroidectomy for Graves' disease and only one patient (2.6%) had a suspected diagnosis of malignancy. Before the widespread adoption of the postoperative PTH level as a predictor of postoperative hypocalcemia, further higher-volume studies, including studies with more diverse pathology, were required to confirm Lindblom et al.'s findings.

Another study limitation was its protocol for postoperative use of calcium supplementation. Patients self-administered calcium supplementation only if they reported symptoms. While this did reflect the practice at that time, this patient-directed calcium supplementation led to inconsistent use of calcium supplementation among the study population and is likely to have decreased the rate of biochemical hypocalcemia at follow-up appointments among symptomatic patients. Further study with protocolized and standardized use of postoperative calcium and vitamin D supplementation was needed to eliminate this confounder.

A final study limitation was the biochemical method used to measure PTH levels. Serum levels of PTH were measured using an Elecsys 2010 assay with a reference range of 1.6–6.9 pmol/L. Inherently, this system had poor accuracy below the reference range. Due to this limitation, Lindblom et al. defined their hypoparathyroidism cutoff point as equal to or lower than the reference range. As this study was focused on hypoparathyroidism, further refinement was necessary, as accurate PTH levels below the reference range may hold additional predictive value.

STUDY IMPACT

At the turn of the millennium, hypocalcemia following total thyroidectomy was one of the main barriers preventing routine, same-day discharge of thyroidectomy patients. The common practice of obtaining serial serum calcium measurements often required a multiday hospital stay. With this in mind, the impact of Lindblom et al.'s landmark paper cannot be understated. Lindblom et al. offered confirmation that postoperative hypocalcemia following total or near-total thyroidectomy was caused by transient hypoparathyroidism. The true innovation of the study was the use of serial measurements of both PTH and serum calcium. By evaluating PTH and serum calcium levels at multiple times during the perioperative period, Lindblom et al. could identify

which lab value was the most predictive of postoperative hypocalcemia. The revelation that postresection PTH level was predictive of both biochemical and symptomatic hypocalcemia allowed for better case hypocalcemia risk stratification and earlier safe hospital discharge. Although future research was required to better characterize the precise predictive PTH levels and the ideal timing of PTH measurements, the underpinning conclusion established avenues for safe same-day discharge for total thyroidectomy patients.

RELEVANT ADDITIONAL STUDIES

Since Lindblom et al.'s article, multiple studies have confirmed intraoperative or postoperative PTH as being a reliable predictor of postoperative hypocalcemia. McLeod et al. demonstrated a postoperative PTH <12 pg/mL predicted the development of hypocalcemia with 100% sensitivity and 92% specificity.[15] Sywak et al. confirmed a low PTH level, ranging between 3 and 10 pg/mL taken 4 hours postoperatively, predicted postoperative hypocalcemia with 90% sensitivity and 84% specificity.[16] Asari et al. reported similarly a PTH less than 15 pg/mL on postoperative day 1 predicted hypoparathyroidism with 97.7% sensitivity and 82.6% specificity.[17] A subsequent 2008 meta-analysis of 27 papers reported postoperative PTH measured at any time within 24 hours of total thyroidectomy accurately predicts the development of hypocalcemia and the need for calcium supplementation.[18]

Building on the predictive value of PTH, multiple large studies using postoperative algorithms to identify and treat temporary hypoparathyroidism post-thyroidectomy showed clinical decision-making, based on post-thyroidectomy PTH levels, could successfully mitigate the risk of symptomatic and biochemical hypocalcemia. In a nonrandomized trial, Wiseman et al. compared postoperative hypocalcemia in thyroidectomy patients managed conventionally, i.e., calcium replacement in response to serum calcium levels or clinical symptoms of hypocalcemia (N = 288), to those stratified by an algorithm that used PTH one hour following surgery to tailor postoperative medical management (N = 135).[19] On multivariate analysis, patients who underwent conventional management had a 2.17 times greater risk of biochemical hypocalcemia during hospitalization (95% confidence interval [CI] 1.20–3.92; $p < 0.01$). Similar findings were presented by Houlton et al.[20] In a case series conducted between March 2008 and November 2009, 180 patients underwent total or completion thyroidectomy. Using a postoperative PTH level >20 pg/mL as a cutoff, 69% of patients were discharged on the day of surgery with zero readmissions for hypocalcemia. These findings culminated in the 2018 American Thyroid Association Statement on Postoperative Hypoparathyroidism: Diagnosis, Prevention, and Management in Adults, where the Surgical Affairs Committee recommended "that a PTH value of 15 pg/ml measured in adults at 30 minutes following thyroidectomy would obviate the need for intensive serum calcium monitoring and/or calcium supplementation, postoperative PTH value of <15 pg/ml would suggest an increased risk for acute hypoparathyroidism that might prompt preemptive prescribing of oral calcium."[21] These changes in clinical practice stem from the seminal results of Lindblom et al.'s landmark paper.

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Chapter 16

Parathyroid Autotransplantation

Review by Helen E. Doran

Landmark Paper

FAILURE OF FRAGMENTED PARATHYROID GLAND AUTOTRANSPLANTATION TO PREVENT PERMANENT HYPOPARATHYROIDISM AFTER TOTAL THYROIDECTOMY

Lorente-Poch L, Sancho J, Muñoz JL, Gallego-Otaegui L, Martínez-Ruiz C, Sitges-Serra A. *Langenbecks Arch Surg.* 2017;402(2):281–287. doi:10.1007/s00423-016-1548-3

RESEARCH QUESTION/OBJECTIVES

Permanent hypoparathyroidism after thyroidectomy is a significant complication. In a meta-analysis of 115 studies, the prevalence of transient hypocalcemia after total thyroidectomy ranged between 19% and 38% and that of permanent hypoparathyroidism between 0% and 3%.[1] Scandinavian and United Kingdom registry data report permanent hypoparathyroidism rates being 4.4% and 3.2%, respectively.[2,3] In certain groups reported rates of permanent hypoparathyroidism are much higher, up to 16% in patients undergoing concomitant central lymph node dissection.[4]

Although there are various established predictors of hypoparathyroidism (extent of surgery, age, vitamin D status, hypermetabolism from Graves' disease, how effectively the compromised parathyroid glands are "splinted" during their recovery),[5] the primary cause is parathyroid dysfunction resulting from intraoperative injury (mechanical or thermal trauma), devascularization, or inadvertent parathyroid removal.

Parathyroid autotransplantation, to attempt restoration of function where in situ preservation is not possible, is variably performed; some surgeons never perform this and others advocate its routine utilization.[6] There is consensus that parathyroid autotransplantation during total thyroidectomy leads to higher rates of postoperative hypocalcemia; it is generally undertaken when the parathyroid glands have been damaged, and reimplanted parathyroid tissue is unlikely to secrete sufficient parathyroid hormone in the initial period after surgery (as the autograft needs sufficient time to revascularize in the muscle pocket used for its reimplantation). However, whether autotransplantation prevents or reduces permanent hypoparathyroidism remains unclear.[7–11] Of most concern is whether autotransplantation contributes to permanent hypoparathyroidism, as has been suggested in a recent meta-analysis,[11] although bias and heterogeneity between the studies was apparent.

 DOI: 10.1201/9781003196211-16

A previous study from Sitges-Serra's group showed that following thyroidectomy, fewer than four parathyroid glands remaining in situ (PGRIS) was a very powerful predictive factor for both protracted and permanent hypoparathyroidism.[5] In this study the rate of permanent hypoparathyroidism in the 143 patients undergoing autotransplantation was higher than that observed in 514 patients not autografted (9.8 vs. 3.1%; $p < 0.002$). A major limitation of this study was failure to consider the influence of glands left in situ in the transplanted group.

Our chosen landmark paper was a more detailed analysis of the subgroup from this paper, with three glands remaining in situ (PGRIS 3). This further analysis both standardized the number of remaining glands and determined whether transplantation per se affects function by comparing the short- and long-term parathyroid function in the PGRIS 3 group after total thyroidectomy, in whom the fourth gland was either autotransplanted (Group Tx) or accidentally resected (Group AR).

STUDY DESIGN

Retrospective cohort study, as cases were identified from a previous study of consecutive patients at an endocrine surgery tertiary referral center undergoing first-time total thyroidectomy for goiter or thyroid carcinoma during the period 2000–2014. The operations were performed by the same team of experienced endocrine surgeons. This earlier study had assessed the relationship between the number of PGRIS and risk of postoperative acute and chronic parathyroid insufficiency. PGRIS was calculated by using the following formula: Four - (number of parathyroid glands autografted + parathyroid glands found in the specimen). Our landmark paper focused on the PGRIS 3 subgroup (three glands remaining in situ) and, using an observational indirect method, compared the short- and long-term parathyroid function in patients in whom the fourth gland was transplanted with a control group in which the gland had been accidentally resected.

The prevalence of postoperative hypocalcemia and protracted and permanent hypoparathyroidism was compared between the two groups. Postoperative hypocalcemia was defined as a serum calcium concentration lower than 2 mmol/L at 24 hours after total thyroidectomy; protracted hypoparathyroidism when intact parathyroid hormone (iPTH) concentration <13 pg/mL and calcium replacement with or without calcitriol was required at 4–6 weeks after thyroidectomy; and permanent hypoparathyroidism was defined as a subnormal iPTH concentration (<13 pg/mL) and need for calcium replacement with or without calcitriol for more than 1 year after total thyroidectomy.

Chi-square or Fisher exact tests were used to compare categorical variables. For quantitative variables, either unpaired student's *t* test and/or U Mann-Whitney test were utilized. Quantitative values were expressed as a mean (standard deviation). Statistical significance was set at $p < 0.05$.

SAMPLE SIZE

From the original series of 669 total thyroidectomies, 186 were PGRIS 3, and these patients are the focus of this landmark paper. In these cases, the fourth

parathyroid gland had been accidentally resected (Group AR) in 76 patients (41%) and autotransplanted (Group Tx) in 110 (59%).

INCLUSION/EXCLUSION CRITERIA

Included were PGRIS 3 cases. Exclusion criteria were less than total thyroidectomies, reoperations, and cases that also underwent a parathyroidectomy for treatment of hyperparathyroidism.

INTERVENTION OR TREATMENT RECEIVED

This study compared outcomes in the PGRIS 3 subset of patients, who were divided retrospectively into two clinically and surgically similar groups: Those for which the fourth gland had been autotransplanted into the ipsilateral sternocleidomastoid muscle (Group Tx, intervention group) and those for which the fourth gland had been inadvertently resected and subsequently found in the specimen by the pathologist (Group AR, control group).

The technique of autotransplantation was a standard technique previously reported by Olson et al.[7] The resected normal parathyroid gland was maintained in a saline humidified gauze on a frozen surface until the end of the procedure for approximately 20–30 minutes. The glands were then chopped into 1-mm^3 fragments and implanted into several pockets in the ipsilateral sternocleidomastoid muscle. All records were collected in a prospectively maintained clinical database. Demographic, disease-related, laboratory, and surgical variables were recorded. All patients were followed up postoperatively for at least 1 year.

RESULTS

From the original series of 669 total thyroidectomies, 186 were PGRIS 3, in which the fourth parathyroid gland had been accidentally resected (Group AR) in 76 patients (41%) and autotransplanted in 110 (59%) (Group Tx). Both groups were comparable in terms of their disease and extent of surgery. The mean postoperative serum calcium levels were comparable (AR: 1.97 ± 0.2 vs. Tx: 1.97 ± 0.22 mmol/L). Rates of protracted (AR: 24% vs. Tx: 25.5%) and permanent hypoparathyroidism (AR: 5.3% vs. Tx: 7.3%) were similar in both groups.

STUDY LIMITATIONS

This study only considered patients in whom most of their parathyroid tissue remained in situ. However, the study showed accidental parathyroidectomy was associated with a risk of permanent hypoparathyroidism in the 5–7% range, well above the 2–3% reported for PGRIS 4 patients, thus confirming removal of only a single gland does affect parathyroid function. Although the viability of the three remaining glands in the resected and the transplanted groups could not be assessed, it is unlikely that there were significant differences with respect to their injury, and this is supported by similar parathyroid failure rates.

The technique of parathyroid reimplantation could have potentially differed from that used by other investigators: whether the gland is autografted immediately or at the end of the thyroidectomy and whether the autotransplanted tissue is fragmented versus injected. Although this might compromise comparisons between studies using different techniques, in this study the technique was standardized between both groups, and extrapolation from the earlier study reporting reduced hypoparathyroidism in the transplanted patients (9.8 vs. 3.1%; $p < 0.002$) supports the technique utilized as being successful.

STUDY IMPACT

The prevalence of parathyroid failure syndromes after total thyroidectomy was similar whether the fourth parathyroid gland was inadvertently excised or autotransplanted. Autotransplantation did not influence the permanent hypoparathyroidism rate. This well-designed landmark paper questions whether autotransplantation of a single parathyroid gland, if it has been devascularized during surgery, is a worthwhile practice during thyroidectomy.

Study strengths included the groups being comparable in terms of pathology; this is important, as some conditions are unequivocally associated with higher rates of permanent hypoparathyroidism. In this study thyroidectomy performed for cancer treatment included routine central compartment lymph node dissection and modified radical lateral neck lymph node dissection, when required. Definitions were clear, and follow-up was standardized and of a sufficient duration (up to 1 year) to determine whether parathyroid gland function would recover.

Study weaknesses included autotransplanted parathyroid gland frozen-section pathology being only performed selectively when the surgeon was in doubt, so there was a small possibility that parathyroid tissue was not transplanted. However, this was unlikely due to the experience of the group.

RELEVANT ADDITIONAL STUDIES

The problem with determining whether parathyroid autotransplantation is effective during thyroidectomy is that it is only undertaken when parathyroid glands have been devascularized and establishing the relative contribution to postoperative parathyroid function from the remaining in situ and autotransplanted glands is difficult.

Inadvertent parathyroidectomy affects postoperative parathyroid function. So it is important to consider inadvertent parathyroid gland removal in these analyses. Lo et al. reported a reduction of the permanent hypoparathyroidism rate in transplanted patients, but the nontransplanted patients had a three-fold rate of inadvertent parathyroidectomy compared to that of transplanted patients.[8]

Comparable results to our chosen landmark paper were reported in a retrospective Italian study[12] that evaluated patients undergoing parathyroid transplantation or inadvertent removal, but with the latter diagnosed by pathology examination. Their control group

(all glands presumed in situ) reported less permanent postoperative hypocalcemia (1%) compared to the transplanted and inadvertent removal groups, 3.5% and 3.4%, respectively. There were a high number of excluded cases – 1,479 (86%) – in this study. Although there were fewer cancer patients in the control group, there was no difference in the proportion of cancer pathology between groups having transplantation or inadvertent removal. The study also evaluated symptoms; change in calcium, phosphate, and PTH over 3 days; and calcium and PTH levels at 6 months postoperatively. Rate and extent of calcium recovery were comparable between groups having transplantation or inadvertent removal. Multivariate analysis showed differences occurred because the recovery in the transplanted and inadvertent removal groups was slower and less marked than in the control group. Importantly, no difference was detected when comparing the transplanted and inadvertent removal groups alone. Therefore, the accidental removal of a parathyroid gland, whether or not it was reimplanted, resulted in a lower and more gradual decrease of the calcium values in the 3 days after surgery when compared with the control patients. Despite these findings, the authors still recommended undertaking autotransplantation, as it is such a safe and easy procedure.

Another earlier and larger retrospective cohort study (1,196 patients) had assessed the proportion of patients developing temporary and permanent hypocalcemia according to the number of transplanted glands.[9] Three hundred and six (25.6%) patients had no parathyroid glands transplanted, 650 patients (54.3%) had one gland autotransplanted, 206 (17.2%) had two glands autotransplanted, and 34 (2.9%) had three glands autotransplanted. They found that temporary hypocalcemia (not requiring calcium supplementation at 6 months postoperatively) is closely and significantly related to the number of autotransplanted parathyroids during total thyroidectomy (increasing with the more glands transplanted). However, the long-term outcome was not affected by the number of parathyroids autotransplanted. They concluded that a "ready selective" approach to parathyroid autotransplantation (i.e., transplanting when there is concern about viability) was an effective strategy for minimizing the risk of permanent hypoparathyroidism.

What all these studies lack is the ability to precisely determine the contribution of the transplanted gland(s) on parathyroid function because of the presence of other potentially functioning glands remaining in situ after thyroidectomy. Confirmation with venous sampling is difficult, particularly if they are reimplanted into the sternocleidomastoid muscle, but may be easier if reimplanted into the forearm. Palazzo et al.'s conclusion that "although some endocrine function from grafted parathyroid fragments may be detectable, it does not follow that it is enough to prevent permanent hypoparathyroidism" is pragmatic and sensible.[9]

Further limitations of most studies include the subjective determinations of surgeons as to whether transplantation is required. Lang et al. reported a higher rate of permanent hypoparathyroidism for cases in which no color change was detected in any of the four parathyroid glands when compared with cases where discoloration of one or two glands was noticed.[13] Most likely this is due to the more detrimental effects of parathyroid ischemia (not resulting in color change) than venous congestion.

The aforementioned recent metanalysis showed parathyroid autotransplantation increases postoperative and protracted hypoparathyroidism, but its influence on permanent hypoparathyroidism is complicated by the period of review, whether the autotransplanted parathyroid glands are fully functioning at the point of postoperative review, the relationship between hypocalcemia and parathyroid function, and whether eventual fibrosis in the transplanted glands is beneficial.[11]

Consideration of the surgical strategy when identifying fewer than four parathyroid glands during total thyroidectomy (an occurrence claimed in up to 15% of operations) is outlined in a retrospective study of thyroidectomy and bilateral central neck dissection, with the eventual conclusion to preserve in situ where possible.[14] In this study of 212 patients with three identified parathyroid glands, parathyroid hormone (PTH) levels at 12 months postoperatively in patients who underwent autotransplantation were significantly lower than patients with all parathyroid glands preserved in situ. This supports Lorente-Poch et al.'s finding that removing one gland affects function.

Avoiding damage to the parathyroid glands during thyroidectomy by meticulous capsular dissection, and possibly surgical adjuncts, is the best strategy to prevent postoperative hypoparathyroidism. This landmark paper sheds doubt on the utility of parathyroid gland autotransplantation to prevent this complication when these glands are devascularized or resected.

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Chapter 17

Epidemiology

Review by Charles Meltzer

Landmark Paper

INCREASING INCIDENCE OF THYROID CANCER IN THE UNITED STATES, 1973–2002

Davies L, Welch HG. *JAMA.* 2006;295(18):2164–2167. doi: 10.1001/jama.295.18.2164

RESEARCH QUESTION/OBJECTIVES

Beginning in the early 2000s, reports from around the world noted that from the 1970s onwards there had been an increase in thyroid cancer incidence accompanied by a stable mortality.[1] This increase was attributed to papillary carcinoma, the most common type of thyroid cancer.[1] In combination with reports that as many as 36% of autopsied individuals had undiagnosed thyroid cancer,[2] increased incidence and stable mortality suggested that many subclinical cancers – or incidentalomas – were being identified. During these three decades, the use of diagnostic modalities expanded dramatically with the advent of widely used thyroid ultrasound, fine needle aspiration cytology (FNAC), CT, positron emission tomography, and MRI. However, disproving or verifying the theory that this increase in incidence was due to over detection of subclinical thyroid cancer was critical to ensuring that patients who needed treatment received it, and that those who did not avoided its associated risks.

The aim of this landmark paper was to determine whether the increasing incidence of thyroid cancer represented an actual change in incidence or resulted from increased diagnostic scrutiny.

STUDY DESIGN

Retrospective cohort evaluation of papillary, follicular, medullary, and anaplastic thyroid cancer diagnosed between 1973 and 2002, using Surveillance, Epidemiology, and End Results (SEER) incidence data from nine areas, representing approximately 10% of the U.S. population, and thyroid cancer mortality data from the U.S. National Vital Statistics System.

SAMPLE SIZE

In 2002, 2,400 cases of thyroid cancer were diagnosed in the nine SEER areas, representing approximately 24,000 new cases nationwide in the U.S.A.

DOI: 10.1201/9781003196211-17

INCLUSION/EXCLUSION CRITERIA

The International Classification of Diseases (ICD) for Oncology (3rd edition) codes for papillary, follicular, medullary, and anaplastic thyroid cancer, encompassing 99.5% of all cancers attributed to the "thyroid" anatomical site in SEER were included. The remaining 0.5% of cases were excluded based on rarity, suspected primary site outside the thyroid, or both.

INTERVENTION OR TREATMENT RECEIVED

Overall thyroid cancer incidence and mortality for each year were age-adjusted to the 2000 population. Incidence trends by type were examined, with medullary and anaplastic thyroid cancer grouped as "poorly differentiated." The size distribution of papillary cancer in 1988 (the earliest year SEER size data were available) and 2002 were compared.

RESULTS

Thyroid cancer incidence increased from 3.6 per 100,000 in 1973 to 8.7 per 100,000 in 2002. The observed 2.4-fold increase (95% confidence interval [CI] 2.2–2.6; $p < 0.001$) was almost entirely due to a 2.9-fold increase (95% CI 2.6–3.2; $p < 0.001$) in papillary cancer incidence from 2.7 per 100,000 to 7.7 per 100,000. No significant changes were observed for follicular or poorly differentiated cancer incidence.

Papillary thyroid cancers measuring ≤1 cm accounted for 49% (95% CI 47–51%) of the increased incidence, and cancers measuring ≤2 cm accounted for 87% (95% CI 85–89%) of the increased incidence. Mortality remained unchanged between 1973 and 2002 at approximately 0.5 deaths per 100,000.

STUDY LIMITATIONS

The primary study limitation is its retrospective observational design. SEER data compiles state, regional, and population-specific cancer registry data.[3] Limitations inherent to SEER data include migration of patients in and out of SEER registry catchment areas and selection bias, both of which can affect long-term outcome measures.[4] In addition, a new World Health Organization classification system introduced in 1988 recommended reclassifying tumors that combine follicular architecture and nuclear features characteristic of papillary carcinoma[5] as papillary carcinoma, affecting 20–30% of all papillary cancers.[6]

The impact of these limitations on mortality outcomes was offset by the use of Centers for Disease Control National Vital Statistics System morality data, which tracks the underlying cause of death from death certificates in each state. However, this data is also subject to limitations related to the coding of cause-of-death information by medical examiners that varies across time periods in studies with very long observation periods.[7] For example, the ICD-9 was introduced for coding cause of death in 1979 and was replaced by the ICD-10 coding system in 1999.[7] The potential impact of these factors is unknown.

STUDY IMPACT

Davies and Welch drew attention, for the first time, to the impact of the widespread use of ultrasound and FNAC in detecting small thyroid nodules and early-stage thyroid cancer and the stable mortality despite increasing incidence. This has reshaped how we should assess sub-centimeter thyroid nodules. The 2015 American Thyroid Association guidelines now provide more cautious workup recommendations that exclude FNAC for nodules <1 cm and recommend the combined use of ultrasound characteristics and clinical risk factors in determining whether biopsy is warranted.[8] In addition the surgical management of thyroid cancer has become more conservative, with the extent of recommended surgery now depending on tumor size, with thyroid lobectomy the current standard for cancers 1–4 cm in size, based on clinical risk factors, ultrasound characteristics, and patient preference.

RELEVANT ADDITIONAL STUDIES

Studies confirmed these findings in other populations. In Canada, the incidence of differentiated thyroid cancer increased by 13% per year between 1990 and 2001.[9] Increases in incidence were statistically significant for tumors ≤2 cm and >4 cm; the authors attributed the latter to the small proportion of patients with large tumors.[9]

In South Korea, with free or inexpensive screening for multiple cancers widely available, thyroid cancer incidence increased 1,500% from 1993 to 2011.[10] The proportion of the population screened for thyroid cancer in 2008–2009 was strongly correlated with the age- and sex-stratified incidence of thyroid cancer across 16 regions,[10] but not with thyroid cancer mortality.[11] Authors from the same institution found that active surveillance for papillary thyroid microcarcinomas, as compared with immediate surgery, was associated with significantly fewer patient reports of neuromuscular, throat and mouth, or scar problems and no greater fear of disease progression.[12]

Other reports suggest that the increasing incidence of thyroid cancers is due in part to other factors. In SEER data from 1992 to 2005, increased diagnostic scrutiny accounted for the increase in tumors <1 cm, or roughly half of the increased incidence of papillary carcinoma.[6] Although this is equivalent to the 49% Davies and Welch attributed to similarly sized tumors, Enewold et al. assumed that more sensitive diagnostic procedures would only affect the detection of very small tumors and suggested that environmental and other risk factors accounted for the increased incidence of larger cancers.[6] Notably, the incidence of cancers >5 cm also increased in this study.[6] It could be argued that the incidence of large tumors would eventually plateau or decrease if detecting smaller cancers fully accounted for the increased incidence of thyroid cancer, which strengthens the argument for investigating other potential causes of increased thyroid cancer incidence.

A 2016 review comprehensively addressed whether the rising thyroid cancer incidence was attributable to increased detection or the role of demographic and environmental risk factors.[13] Nonmodifiable risk factors for thyroid cancer include female sex, younger age, white non-Hispanic race/ethnicity, and family history of thyroid cancer.[13] Other risk factors are modifiable such as childhood radiation exposure, which is a known risk factor

for the later development of thyroid cancer. However, exposure to ionizing radiation after age 20 has little effect on the risk of developing thyroid cancer.[13] The relationship between obesity and thyroid cancer is well documented.[13,14] In 2013–2015, an estimated 16% of all papillary thyroid cancers and 63% of large papillary cancers diagnosed in the United States were attributable to overweight and obesity.[15] In addition, overweight and obesity are associated with more aggressive tumors.[13] A related risk factor is adult height, with a dose-response association between taller height and increased risk of thyroid cancer for both men and women.[16]

Rates of cigarette smoking have declined from 37.4% to 22.5% during the period of the landmark paper[17] and may have affected the incidence of thyroid cancer.[13] Cigarette smoking was associated with an approximately 20% reduction in the risk of developing thyroid cancer in a meta-analysis of international studies.[18] The mechanism is unclear but may be related to cigarette extracts acting as partial agonists for thyroid hormone receptors.[18]

Robust epidemiological studies are needed to further elucidate the etiology of thyroid cancer by distinguishing between factors involved in the development of disease and those related to increased access to healthcare and screening.[13,14]

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Chapter 18

Non-Invasive Follicular Thyroid Neoplasm with Papillary-like Nuclear Features (NIFTP)

Review by Tal Yalon and Haggi Mazeh

Landmark Paper

NOMENCLATURE REVISION FOR ENCAPSULATED FOLLICULAR VARIANT OF PAPILLARY THYROID CARCINOMA: A PARADIGM SHIFT TO REDUCE OVERTREATMENT OF INDOLENT TUMORS

Nikiforov YE, Seethala RR, Tallini G, Baloch ZW, Basolo F, Thompson LDR, Barletta JA, Wenig BM, Ghuzlan AA, Kakudo K, Giordano TJ, Alves VA, Khanafshar E, et al. *JAMA Oncol.* 2016;2(8):1023–1029. doi:10.1001/jamaoncol.2016.0386

RESEARCH QUESTION/OBJECTIVES

The follicular variant of papillary thyroid carcinoma (FVPTC) is a tumor composed of neoplastic follicles rather than papillae, with follicular cells showing nuclear features characteristic of papillary thyroid carcinoma (PTC). This tumor is subdivided into infiltrative and encapsulated subtypes. While the first demonstrates features of invasion, the latter lacks these features and therefore raises the question of its malignant potential.

The aim of this landmark study was to re-examine the tumor type previously known as an encapsulated follicular variant of papillary thyroid carcinoma (EFVPTC) through a review of a set of cases with long follow-up in order to establish standardized diagnostic criteria and identify terminology that would most appropriately address both its biological behavior and clinical characteristics.

STUDY DESIGN

An international multi-institutional, multidisciplinary workgroup that retrospectively reviewed thyroid tumors diagnosed as EFVPTC.

SAMPLE SIZE

Two hundred and sixty-eight thyroid tumors were diagnosed as EFVPTC by the histological criteria known at the time of the study (2016).

DOI: 10.1201/9781003196211-18

INCLUSION CRITERIA

Thyroid tumors diagnosed as EFVPTC based on the histological criteria that consisted of an encapsulated or well-circumscribed nodule, a follicular growth pattern with no well-formed papillae, and nuclear features of PTC.

INTERVENTION OR TREATMENT RECEIVED

Patients were divided into two groups: Group 1 (n = 138) included patients with noninvasive EFVPTC who did not receive radioactive iodine (RAI) and were followed up for at least 10 years, and Group 2 (n = 130) included patients with EFVPTC who demonstrated capsular invasion and/or vascular invasion and were followed up for at least 1 year. Through a series of blinded histological evaluations and molecular analysis, a 3-point nuclear score (range 0–3) was developed using random effect logistic regression. All tumors were evaluated by 22 blinded pathologists, who through a series of face-to-face meetings and teleconferences, established consensus diagnostic criteria and developed a new nomenclature.

After the exclusion of 29 patients due to insufficient diagnostic nuclear features of PTC; presence of invasion; or features of classical, solid variant, or poorly differentiated PTC, Group 1 included 109 patients. In Group 2, 29 patients were excluded on the basis of at least 1% papillary growth, infiltrative borders, lack of nuclear features of PTC, or lack of invasion, leaving 101 patients.

RESULTS

All 109 patients from Group 1 were alive and had no evidence of disease during an observation period of 10–26 (mean 14.4) years. In Group 2, 85 patients were treated with RAI. During an observation period of 1–18 (mean 5.6) years, five patients developed distant metastasis, two of whom died from their disease. One patient who had lymph node metastasis had persistent disease, and five patients had detectable serum thyroglobulin levels.

Based on the results of Group 1, the name non-invasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP) was proposed and adopted. A simplified and reproducible criterion for nuclear features that could assist with the diagnosis of NIFTP by routine pathology practice was developed. This 3-point scoring system delivered an accurate classification, with a score of 0–1 diagnostic for benign nodules and a score of 2–3 diagnostic for NIFTP, with a sensitivity of 98.6% (95% confidence interval [CI], 96.3–99.4%), specificity of 90.1% (95% CI 86.0–93.1%) and overall classification accuracy of 94.3% (95% CI, 92.1–96%).

STUDY LIMITATIONS

This study is very well constructed from a methodological perspective; however, it still has several limitations. First and foremost, it is a retrospective study that does not have further validation of its results. In addition, although the follow-up period was significant,

for proper clinical application, a lengthier follow-up period would have been preferable. This is especially true for Group 2 in which the mean follow-up period was 5.6 (range 1–18) years, a relatively short period, as opposed to Group 1 that had a mean follow-up time of 14.4 (range 10–26) years. Lastly, this study has a major impact on the surgical and nonsurgical management of patients diagnosed with NIFTPs. However, it did not provide any practical guidance in terms of their postoperative management, follow-up and surveillance.

STUDY IMPACT

This paper tackled a very controversial pathological diagnosis, first by re-examining a group of patients with the diagnosis of FVPTC by means of pathological diagnosis, clinical course, and clinical outcome. In addition, this study provides reproducible and simplified histopathological diagnostic criteria. Lastly, although it may seem like semantics to some, this article proposed the name NIFTP as a replacement for the problematic definition of EFVPTC. Given its indolent nature, there has been a long-lasting debate regarding the classification of encapsulated (noninvasive) FVPTC as cancer. Nikiforov et al. introduced this significant nomenclature change, suggesting the term NIFTP. This change of nomenclature omits from the diagnosis misleading words such as "cancer" and "carcinoma," with the aim of eliminating the intuitive stigma of malignancy implied by the previous terminology.[1]

The term NIFTP was first accepted in 2017 by the World Health Organization, introducing it in addition to the categories of malignant and benign neoplasms. This was later revised in 2022, and to date, the category of borderline thyroid tumors includes NIFTP, thyroid tumors of uncertain malignant potential (UMP), and hyalinizing trabecular tumors (HTT). These neoplasms have the potential to develop metastasis, but the likelihood of such occurrences is extremely low.[2] The term NIFTP was soon adopted in consensus statements and practice guidelines such as those of the American Thyroid Association (ATA), American Association of Endocrine Surgeons (AAES), and Endocrine Section of the American Head and Neck Society (AHNS).[3–5] From a practical surgical perspective, even prior to this nomenclature change, the recommended surgical treatment for EFVPTC, as stated in the 2015 ATA guidelines, was that such pathology can be treated with lobectomy alone. Nevertheless, this change has had a significant impact on relieving patients' anxiety, in addition to a potential reduction of overtreatment.[6]

RELEVANT ADDITIONAL STUDIES

The clinical outcomes of patients diagnosed with NIFTP was addressed by several studies. Among them is a study by Eskander et al. published in 2019.[7] This group examined retrospectively the incidence of NIFTP and predictors of disease-free survival. In their retrospective cohort from Ontario, Canada, 725 patients with FVPTC were included, of which 318 patients were reclassified as NIFTP. During a median follow-up period of 15.3 years, 9.4% of the patients with NIFTP developed a locoregional recurrence, which is significantly higher than described by Nikiforov et al. in 2016. Bongiovanni et al. published a systemic review and meta-analysis in 2019 that aimed to

estimate the risk of malignancy among all surgical patients when considering NIFTP as a malignant versus a nonmalignant entity. In addition, they examined the prevalence of NIFTP among patients with a preoperative fine needle aspiration (FNA) diagnoses of Bethesda V or VI.[8] This meta-analysis included nine studies with 13,752 patients, of which NIFTP was identified in 696 patients (5%). The prevalence of malignancy in this meta-analysis was 45.7%, and when NIFTP was considered nonmalignant, the pooled rate of malignancy reduction was 5.5%. Interestingly NIFTP was found in 14% and 3% of patients with FNA diagnoses of Bethesda V and VI, respectively. In addition, the 2017 update of the Bethesda System for Reporting Thyroid Cytopathology presented two different risk of malignancy (ROM) estimates for each of its diagnostic groupings. In one of these ROM estimates NIFTP was considered malignant, and in the other it was considered a benign pathological diagnosis.[9]

Overall, this paper by Nikufirov et al. is considered a landmark due to the substantial paradigm shift in the treatment of these more indolent thyroid tumors that it directed.

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Chapter 19

Papillary Microcarcinoma

Review by Timothy M. Ullmann and Quan-Yang Duh

Landmark Paper

AN OBSERVATIONAL TRIAL FOR PAPILLARY THYROID MICROCARCINOMA IN JAPANESE PATIENTS

Ito Y, Akira Miyauchi A, Inoue H, Fukushima M, Kihara M, Higashiyama T, Tomoda C, Takamura Y, Kobayashi K, Miya A. *World J Surg.* 2010;34(1):28–35. doi: 10.1007/s00268-009-0303-0

RESEARCH QUESTION/OBJECTIVES

Papillary thyroid carcinoma (PTC) is often an indolent disease. Autopsy studies have demonstrated that papillary thyroid microcarcinomas (PTMCs), defined as tumors <1 cm in maximal diameter, have a prevalence upwards of 30%.[1] These findings raised concern that small occult tumors are being overtreated. In 2003, a group of surgeons from Kuma Hospital in Kobe, Japan demonstrated the feasibility of active surveillance for selected patients with PTMC.[2] However, that cohort was small; it included only 162 patients in the observation group. Thus, many concerns remained about the safety of observation for these patients on a larger scale, especially in comparison to the standard-of-care up-front resection. To better assess the relative safety of observation versus up-front surgery for patients with PTMC, the authors designed this landmark follow-up study, which expands upon the original observation cohort and adds to an up-front surgery comparison group.[3]

STUDY DESIGN

The study was a prospective observational cohort study performed at a single center, Kuma Hospital in Kobe, Japan. Observation consisted of semiannual ultrasound, with growth ≥3 mm on serial ultrasound or development of lymphadenopathy considered progressive disease indicating a need for surgery. Patients opting for observation were compared to those who chose up-front surgery, with the primary outcome being disease progression.

SAMPLE SIZE

Three hundred and forty patients chose to undergo observation and 1,055 underwent up-front surgery during the study period.

 DOI: 10.1201/9781003196211-19

INCLUSION/EXCLUSION CRITERIA

Consecutive patients diagnosed by fine needle aspiration biopsy (FNAB) with PTMC between 1993 and 2004 were considered for enrollment. Patients with localized PTMCs without evidence of regional spread, abutment of the trachea or posterior capsule, or aggressive features by FNAB were included and offered observation. Those patients who had evidence of locally advanced disease at diagnosis were treated surgically and included in the surgery group. Patients with distant metastases at the time of diagnosis were excluded.

INTERVENTION OR TREATMENT RECEIVED

Patients who chose observation were followed with semiannual ultrasound. Those patients whose tumors grew by 3 mm or more from the size at diagnosis, or those who developed lymph node metastases, were advised to undergo surgical resection. Patients opting for up-front surgery or those with locally advanced disease at diagnosis were treated with partial or total thyroidectomy, with or without lymphadenectomy, at the discretion of the treating surgeon.

RESULTS

During the study period, 340 patients (314 females and 26 males) were initially managed with observation, and 1,059 patients (964 females and 95 males) were treated with up-front surgical resection. Figure 19.1 shows patient outcomes by initial treatment. Mean follow-up was 74 months for the observation group and 76 months for the initial surgical resection group. Two patients died of thyroid cancer in the study period; both were in the surgery group and had lymphatic metastases at the time of diagnosis.

In the observation group, 31 patients (9.1%) had tumors that grew at least 3 mm during the study period, and 7 patients (2.1%) developed new lymphatic metastases. However, 109 patients (32%) in the observation group eventually had surgery for their cancers. The majority of these patients had their cancers resected due to growth (32 patients, 9.4%), unknown reasons (25 patients, 7.3%), or tumor location near the recurrent laryngeal nerve (17 patients, 5.0%). Notably, of the 32 patients who elected to have surgery due to tumor growth following observation, only 15 of them had growth ≥3 mm. Conversely, of the 31 patients whose tumors did grow at least 3 mm, 18 underwent surgery and 13 did not. Importantly, 7 (53.8%) of the 13 patients who did not undergo surgery for tumor growth had a subsequent decrease in the size of their tumors over time.

Among the 1,055 patients who had up-front surgery, lobectomy was the most common operation (490 patients, 46.4%); 536 patients (50.8%) underwent central neck dissections and 425 (40.3%) underwent at least a unilateral modified radical neck dissection. Only 94 patients (8.9%) had no lymphadenectomy performed. The overwhelming majority of patients had no clinical evidence of nodal metastases (909 patients, 85.8%). Thirty-two patients (3.0%) developed recurrent disease during the study period. The majority of these recurrences were in lymph nodes (26 patients, 81.3%), with the next most common site being thyroid (6 patients, 18.8%).

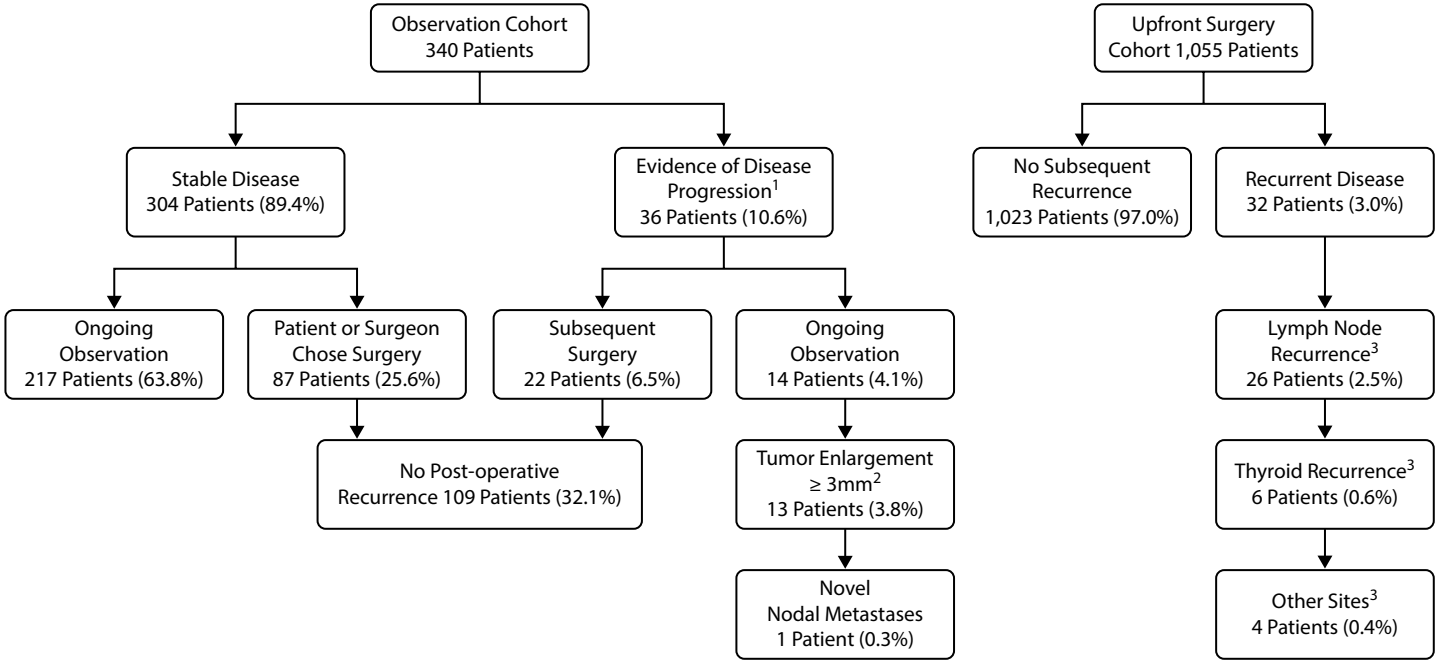

Figure 19.1 Consort diagram of outcomes by initial treatment. (1) Tumor growth ≥3 mm or development of novel nodal metastases. (2) Seven of thirteen patients observed after tumor growth ≥3 mm demonstrated decrease in tumor size on follow-up ultrasound. (3) These categories are not mutually exclusive.

Critically, the authors compared the rate of recurrent disease in the surgery group to the rate of novel nodal metastasis in the observation cohort and found no significant difference (32 patients [3.0%] vs. 7 patients [2.1%]). Furthermore, the authors compared the rate of lymph node recurrence between patients who did and did not undergo lateral neck dissection and found no difference. Two patients in the study developed distant metastases; both were in the immediate surgery group.

STUDY LIMITATIONS

The main limitation of this study is the lack of randomization of treatment offered; thus, there is likely a selection bias for patients with less aggressive disease choosing observation versus immediate surgery. Therefore, it is not possible to definitively conclude that observation is noninferior to surgical resection based on the data included in this study. Furthermore, the group of patients offered observation was different from the comparison cohort who were treated with immediate resection, as the latter group includes patients with locally advanced disease. This becomes an important consideration when comparing recurrence rates after surgery with the development of novel lymphatic metastases in the observation cohort, as this surgery group had patients with more advanced disease and higher risk of recurrence at diagnosis.

Additionally, there are limitations with regard to generalizability of these results to other patient populations. The majority of surgical patients (91.1%) had central, lateral, or multiple compartment lymph node dissections despite the low prevalence of clinically evident lymph node metastases. In the United States, prophylactic lymphadenectomy is rarely performed and generally discouraged, especially for small papillary cancers.[4] Therefore, it is unclear how the observations of this landmark paper might translate to patients treated with lobectomy in the United States. Similarly, 40.9% of patients in the surgery group and 44.0% of patients in the observation group who went on to have surgery were treated with total thyroidectomy. The American Thyroid Association (ATA) changed their guidelines in 2015 to recommend lobectomy alone for patients with intrathyroidal PTMCs, so the majority of these patients would likely have been treated with lobectomy in the United States. Thyroid-stimulating hormone (TSH) suppression was at the discretion of the treating physicians and is not well described in the article. Finally, adjuvant radioactive iodine treatment was not used in this study cohort, which may have increased recurrence rates.

STUDY IMPACT

PTC has become one of the most common malignancies worldwide, due in part to the increase in availability of ultrasound and the subsequent detection of subclinical thyroid tumors. However, the majority of these newly diagnosed tumors are small and indolent; in fact, most newly diagnosed PTMCs may never become clinically meaningful thyroid cancers.[5] Thus, if all patients with PTMC were treated with surgical resection, the majority may not derive any benefit. It was this understanding

that drove the authors to design a prospective study of active surveillance for patients with PTMC.

This landmark paper was among the first to demonstrate safety and feasibility in a large cohort of patients undergoing active surveillance for low-risk PTMCs compared to up-front surgical resection. In light of these results, the ATA adjusted guidelines for treatment of PTMCs in 2015, suggesting that an "active surveillance management approach can be considered as an alternative to immediate surgery" for patients meeting the criteria in this paper.[4] Since its publication, without doubt many patients have avoided surgery that likely would have offered them little to no benefit. Subsequent studies from other groups around the world have supported the safety of selective active surveillance for these patients, and current research is focused on extending the criteria for active surveillance as well as improving patient selection.

RELEVANT ADDITIONAL STUDIES

The results demonstrated by the group from Kuma Hospital sparked a major international interest in studying surveillance for PTMCs. A follow-up study from the same group aimed to address predictors of disease progression in this cohort, with particular attention to patient age.[6] They found that young age was an independent predictor of PTMC progression (growth or development of nodal metastases), with patients 60 years of age and older having only a 4% incidence of tumor growth and 0.5% incidence of novel nodal metastases at 10 years of observation. In contrast, 12.1% of patients younger than 40 had tumor growth ≥3 mm and 16.1% developed novel nodal metastases by 10 years. Crucially, older patients are at higher risk of complications from surgery and anesthesia and are therefore arguably the best candidates for active surveillance from a risk-benefit standpoint.

Others have sought to refine the definition of tumor growth and identify better predictors of disease progression. A group from Memorial Sloan Kettering Cancer Center published a paper on their cohort of 291 patients undergoing observation for papillary thyroid cancer.[7] Importantly, they extended the inclusion criteria to patients with tumors as large as 1.5 cm in maximal diameter and found no difference in growth rates between PTMCs less than 1.0 cm and tumors from 1.0 to 1.5 cm. The authors assessed tumor growth in three dimensions and calculated tumor volume, finding it to be both an earlier and more accurate predictor of disease progression than growth ≥3 mm in a single dimension.

Future studies are likely to both expand the criteria for patients who may opt for active surveillance over surgery and improve prognostication and identification of those at risk for disease progression. Molecular testing offers one such opportunity; treatment options may be further personalized if future studies are able to correlate genotype with phenotypic behavior of PTMCs. Observation for small-volume recurrent disease in the central and lateral neck represents an additional opportunity to reduce performance of potentially unnecessary surgery. While there remains room for refinement, it is clear that active surveillance can be a safe and viable option for select patients diagnosed with PTMC, and it is likely to become increasingly common in the future.

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Chapter 20

Risk Stratification

Review by Nancy L. Cho and Gerard M. Doherty

Landmark Paper

USING THE AMERICAN THYROID ASSOCIATION RISK-STRATIFICATION SYSTEM TO REFINE AND INDIVIDUALIZE THE AMERICAN JOINT COMMITTEE ON CANCER EIGHTH EDITION DISEASE-SPECIFIC SURVIVAL ESTIMATES IN DIFFERENTIATED THYROID CANCER

Ghaznavi SA, Ganly I, Shaha AR, English C, Wills J, Tuttle RM. *Thyroid.* 2018;28(10):1293–1300. doi: 10.1089/thy.2018.0186

RESEARCH QUESTION/OBJECTIVES

Appropriate surgical and medical treatment of differentiated thyroid cancer (DTC) patients depends on accurate risk stratification that is based upon the risk of disease recurrence and disease-specific survival (DSS).[1] The eighth edition of the American Joint Committee on Cancer (AJCC) staging system recently raised the age cutoff for patients with DTC from 45 years to 55 years, thereby downstaging approximately one-third of patients into stage I or II categories (absence or presence of distant metastatic disease, respectively). This reclassification raises concern that risk stratification may no longer be accurate, especially for American Thyroid Association (ATA) high-risk patients who are moved into this younger cohort by virtue of their age, despite other markers of disease process and biology.[2,3] The aim of this study was to integrate the ATA risk stratification system with the AJCC staging categories to further refine DSS for the younger cohort of patients (<55 years old) and improve prediction of outcomes based on disease behavior and not just age alone.

STUDY DESIGN

A retrospective cohort study (1980–2016) was performed using the Memorial Sloan Kettering Cancer Center (MSKCC) tumor registry to assign DTC patients an eighth edition AJCC stage (I or II), ATA risk of recurrence (low, intermediate, or high), and age group at diagnosis (younger patients ≤45 years and older patients 45–55 years) and correlate with 10-year DSS.

SAMPLE SIZE

A total of 4,881 adult DTC patients aged <55 years receiving treatment MSKCC at any time point during their disease course.

 DOI: 10.1201/9781003196211-20

INCLUSION/EXCLUSION CRITERIA

All adult DTC patients who received any treatment at MSKCC from 1980 to 2016 were included in the study patient population. All patients older than 55 years, with less than 2 years of follow-up from the time of tumor diagnosis, with anaplastic or medullary thyroid cancer and with incomplete data for staging or recurrence risk determination were excluded.

INTERVENTION OR TREATMENT RECEIVED

Patients were assigned an AJCC stage (I or II) based on the absence or presence of distant metastatic disease; ATA risk of recurrence (low, intermediate, or high) according to the original 2009 ATA risk stratification system; and age group at diagnosis (younger patients ≤45 years and older patients 45–55 years). Additional clinical variables were collected including sex, histological subtype, tumor size, presence/absence of minor or gross extrathyroidal extension, and lymph node status. The primary outcome was DSS over 10 years stratified by AJCC stage, ATA risk of recurrence, and age group.

RESULTS

Of the 4,881 patients included in the study population, there were 122 disease-related deaths (2.5%) over a median follow-up of 6.6 years. Most patients were female (73%), diagnosed with papillary thyroid cancer (96%), and were AJCC stage I (98%). A total of 1,799 (37%) patients were ATA low risk, 2,692 (55%) were ATA intermediate risk, and 390 (8%) were ATA high risk. When stratified by age, 3,167 (65%) were ≤45 years old (3,131 stage I, 36 stage II) and 1,714 (35%) were 45–55 years old (1,666 stage I, 48 stage II).

Of 122 disease-specific deaths, 96/4,797 (2.0%) occurred in stage I patients and 26/84 (31%) occurred in stage II patients. There were no disease-specific deaths among ATA low-risk patients. There were 59/2,692 (2.2%) disease-specific deaths among ATA intermediate-risk patients and 63/390 (16.2%) deaths among ATA high-risk patients. Kaplan-Meier survival curves showed excellent 10-year DSS for stage I patients (98%), but worse than expected 10-year DSS for stage II patients (68%), $p < 0.0001$. Similarly, ATA low- and intermediate-risk patients demonstrated excellent 10-year DSS (100% and 98%) compared to ATA high-risk patients (87%), $p < 0.0001$.

When integrating ATA risk categories with AJCC staging,

- Stage I low-risk and intermediate-risk patients had excellent 10-year DSS (100% and 98%).
- Stage I high-risk and stage II high-risk patients had worse 10-year DSS outcomes (92% and 68%, respectively), $p < 0.0001$.
- Stage I ATA high-risk patients 45–55 years of age had worse 10-year DSS (89%) compared to younger patients <45 years old (95%), $p = 0.002$.
- Stage II ATA high-risk patients 45–55 years of age also had worse 10-year DSS (61%) compared to younger patients <45 years old (78%), $p = 0.044$.

Overall, the authors identified six categories with progressively worse DSS as AJCC stage, ATA risk, and age increased (Table 20.1).

Table 20.1 Subgroups of Patients Demonstrating Progressively Worse 10-Year DSS with Increasing AJCC Stage, ATA Risk, and Age

Category (AJCC stage, ATA risk, age)	10-Year Disease-Specific Survival
Stage I, low, < 55 years	100%
Stage I, intermediate, < 55 years	98%
Stage I, high, < 45 years	95%
Stage I, high, 45–55 years	89%
Stage II, high, < 45 years	78%
Stage II, high, 45–55 years	61%

STUDY LIMITATIONS

This study was a retrospective study, so is limited by data available in the MSKCC tumor registry. As such, some clinicopathological features that are important for ATA risk stratification (vascular invasion, size/number of lymph node metastases, extent of gross extrathyroidal extension) were not available for inclusion in the analysis. Also, as a tertiary referral center, MSKCC data may be prone to referral bias, as patients treated at this institution may have more advanced thyroid cancer. Similarly, patients included in the cohort were treated by various endocrinologists and surgeons with heterogeneous use of adjuvant radioactive iodine and varriable surgical expertise, potentially resulting in inconsistent patient outcomes. Finally, thyroid cancer mortality may extend beyond the 10-year DSS used as the primary outcome and fail to be captured in the study analysis, although this likely represents a small proportion of the cohort.

STUDY IMPACT

In our current era of precision medicine, one-size treatment does not fit all. In this landmark paper Ghaznavi et al. highlighted the challenges of accurate thyroid cancer risk stratification when patients with a broad range of disease are categorized together in the same AJCC stage group. The eighth AJCC reclassification raised the age cutoff for stage I DTC patients from 45 to 55 years of age at the time of diagnosis, thus underestimating the risk of mortality for a select group of patients with high-risk disease; this is especially relevant for a disease process with age at diagnosis as a major determinant of survival.[4,5] The authors sought to address this challenge by integrating AJCC staging with ATA risk classification to refine predictions of DSS. While the 10-year DSS survival was not significantly impacted for many patients, a subset of patients (stage I high-risk 45–55 years old, stage II high-risk <45 years old, and stage II high-risk 45–55 years old) did have significantly worse 10-year DSS than expected. Not surprisingly, high-risk features, including gross extrathyroidal extension for stage I patients and distant metastases for stage II patients, were associated with increased mortality and decreased 10-year DSS for these subsets of patients accordingly.[6,7]

The authors identified six subgroups of patients based upon AJCC stage, ATA risk, and age in order to provide valuable survival data that is more individualized and disease-specific, especially with respect to ATA high-risk patients and those 45–55 years of age. As a result, risk stratification can be more accurately defined for DTC patients despite

the widened spectrum of disease included in the younger prognostic stage groups due to the AJCC reclassification. This refined approach paves the way for further re-evaluation of risk stratification for DTC patients that is much more robust and inclusive of the available data at hand. Future adjustments in risk stratification may also integrate molecular profiling, race, gender, and dynamic risk assessment at follow-up into the overall system.

RELEVANT ADDITIONAL STUDIES

While most DTC patients will respond very well to surgery with or without radioactive iodine ablation, a subset of patients may benefit from further individualized risk assessment that accounts for AJCC stage, ATA risk, and additional information available such as molecular drivers of their disease biology. The Cancer Genome Atlas recently described the genomic landscape of thyroid carcinoma, thereby increasing our understanding of driver mutations responsible for the majority of DTC cases and allowing for further risk stratification and appropriate clinical management for these patients.[8] Many of these drivers can be assessed preoperatively and may influence surgical decision-making (lobectomy vs. total thyroidectomy ± central neck dissection) as well as patient counseling regarding prognosis and future treatment options. However, it is important to note that the presence of specific mutations (*BRAF*^{V600E}) does not always predict poor outcome; further prospective studies are needed to evaluate the impact of surgery/adjuvant treatment with mutational profiles on outcomes.[9,10]

In addition to molecular data, Tuttle et al. proposed a dynamic risk assessment to include ongoing patient follow-up data to evaluate DSS over time.[11] Additional clinical factors, including response to therapy, thyroglobulin levels, and the presence of persistent/recurrent disease, can be included along with the initial risk stratification to further individualize DSS estimates. This dynamic assessment becomes particularly relevant for patients electing to undergo active surveillance of low-risk disease or in the presence of low-volume disease, where surgery may not be the first line of treatment. Future refinement of risk stratification should consider all available information, including molecular profiling and patient demographics, to determine the optimal strategy for treating DTC patients in the current era of precision medicine.

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Chapter 21

Staging

Review by Bianka Saravana-Bawan and Jesse D. Pasternak

Landmark Paper

AN INTERNATIONAL MULTI-INSTITUTIONAL VALIDATION OF AGE 55 YEARS AS A CUTOFF FOR RISK STRATIFICATION IN THE AJCC/UICC STAGING SYSTEM FOR WELL-DIFFERENTIATED THYROID CANCER

Nixon IJ, Wang LY, Migliacci JC, Eskander A, Campbell MJ, Aniss A, Morris L, Vaisman F, Corbo R, Momesso D, Vaisman M, Carvalho A, Learoyd D, et al. *Thyroid.* 2016;26(3): 373–380. doi: 10.1089/thy.2015.0315

RESEARCH QUESTION/OBJECTIVES

Prior research has demonstrated that survival outcomes for patients diagnosed with well-differentiated thyroid cancer (WDTC) are dependent upon age, with younger patients having improved outcomes in comparison to older patients with disease of the same extent.[1] Due to this difference in outcomes, age was incorporated into the American Joint Committee on Cancer/Union for International Cancer Control (AJCC/UICC) staging system for WDTC. Under this system, all WDTC patients with cancer confined to their neck (did not have distant metastasis) had stage I disease if they were younger than 45 years of age. For older patients, stage is assigned from Stage I to Stage IV based on tumor size, nodal, and distant metastatic (TNM) involvement.[2]

Since the publication of the AJCC/UICC guidelines in 2010, further large datasets have consistently shown that even older patients continue to have excellent outcomes. Specifically, observations show that up to the age of 55 years, patients demonstrate an improved survival compared to older matched cohorts.[3] A large cohort study from Memorial Sloan Kettering Cancer Center (MSKCC) suggested an alteration in the age cutoff to classify the lower-risk WDTC group to younger than 55 years, instead of the previously described 45 years.[4] This multi-institutional landmark paper aimed to validate this proposed age cutoff change in the WDTC AJCC/UICC staging system in a larger and more comprehensive patient cohort.

STUDY DESIGN

A retrospective, multi-institutional international cohort study was performed across ten institutions, with institutional-based data collected by clinicians by chart review. The date range of data collection varied by institution, based on availability of high-quality reliable data.[4]

DOI: 10.1201/9781003196211-21

SAMPLE SIZE

Overall, 9,484 patients who were treated across the ten different institutions, from four countries, for WDTC were included for analysis.[4]

INCLUSION/EXCLUSION CRITERIA

Those patients with a diagnosis of WDTC, reliable data regarding TNM characteristics, age at first treatment, disease-specific survival (DSS) status, and time to last follow-up were included in the study population.

Patients who could not be staged by AJCC/UICC based on the data provided by the respective institutions were excluded. Patients included in the original 1986–2005 MSKCC cohort analysis, which led to the proposal of age change from < 45 to < 55 years in AJCC/UICC staging model, were also excluded.[4]

INTERVENTION OR TREATMENT RECEIVED

All patients were assigned an AJCC/UICC stage with the guidelines, using 45 years as a cutoff, and then restaged using an age of 55 years as the cutoff. The AJCC/UICC prognostic stage groups under the eighth edition are outlined in Table 21.1. DSS was assessed using the Kaplan-Meier method, and a concordance probability estimate (CPE) was applied to quantify concordance between stage and observed outcome within each model.

Patients who had been included in previous studies with analysis regarding age cutoff for thyroid cancer staging were excluded and a planned subgroup analysis was performed as a means to check for confirmation bias. Analysis of survival for patients who were downstaged as a result of the age cutoff being 55 years as compared to 45 years was carried out.[4]

RESULTS

From the ten institutions, a total of eight datasets that included 9,484 patients were reviewed. The median patient follow-up was 5.3 years (range 0–44 years), and median

Table 21.1 Eighth Edition American Joint Committee on Cancer Differentiated Thyroid Cancer Stage Groups

Age at Diagnosis	T	N	M	Stage
< 55 years	Any T	Any N	M0	I
	Any T	Any N	M1	II
≥ 55 years	T1	N0 / NX	M0	I
	T1	N1	M0	II
	T2	N0 / NX	M0	I
	T2	N1	M0	II
	T3z / T3b	Any N	M0	II
	T4a	Any N	M0	III
	T4b	Any N	M0	IVA
	Any T	Any N	M1	IVB

patient age was 45 years (range 4–96 years). The 10-year DSS for the entire study population was 96.6%, with 224 patients dying due to their disease. A large portion of the cohort had small primary tumors and were lymph node negative (49.1%: T1 and N0/NX 69.7%). Few patients harbored metastatic disease, with 97.4% being classified as M0/MX.

Utilizing AJCC/UICC staging with 45 years as the age cutoff resulted in 6,600 (69.6%) of patients being classified as Stage I, 741 (7.8%) as Stage II, 1,230 (13%) as Stage III, and 913 (9.6%) as Stage IV. Associated 10-year survival for this classification was 99.7%, 97.3%, 96.6%, and 76.3%, by stage. In comparison, applying AJCC/UICC staging with 55 years as the age cutoff resulted in 7,736 (81.5%) of patients being classified as Stage I, 444 (4.7%) as Stage II, 707 (7.5%) as Stage III, and 600 (6.3%) as Stage IV. Associated 10-year survival rates by stage in escalating order were 99.5%, 94.7%, 94.1%, and 67.6%.

Raising the age cutoff resulted in downstaging to Stage I of 1,136 (12.3%) patients. Overall, 329 (3.5%) patients changed from Stage II, 523 (5.5%) patients changed from Stage III, and 284 (3.0%) patients had been Stage IV.

Revised Staging Translates to Better Outcomes

With revised staging with the age cutoff of 55 years, those patients with T2N0M0 disease who were downstaged from Stage II to Stage I had improved outcomes compared to those patients who remained classified as Stage II disease (10-year DSS 99.1% vs. 95.9%, $p = 0.027$). Patients with T3N0M0 or T1-3N1aM0 disease who were downstaged from Stage III to Stage I disease similarly had improved outcomes compared to those patients who remained classified as Stage III disease with the cutoff of 55 years (10-year DSS 99.6% compared to 94.1%, $p < 0.001$). Stage IV patients with advanced local (T4) or regional (N1b) disease with M0 status that were downstaged to Stage I disease with increased age cutoff of 55 years also had good outcomes (10-year DSS 94.8%). In contrast, downstaging the 29 patients (0.3%) with Stage IV disease with M1 status to Stage II disease had a (nonsignificantly) worse prognosis compared with the conventional Stage IV group (10-year DSS 67.6% vs. 75.5%, $p = 0.7$).

When determining if the new age cutoff was a valuable tool, using CPE calculation demonstrated improvement for AJCC staging with an age cutoff of 55 years as compared to 45 years. The CPE represents the concordance between the disease stage and the patient outcome, or survival, given the staging model. The CPE in this study estimated how well staging, using an age cutoff of 55 years compared to 45 years, accurately estimates 10-year DSS. The CPE was 0.92 (standard error 0.01) in the older age cutoff compared to 0.90 (standard error 0.02) for the younger cutoff.

STUDY LIMITATIONS

Overall, the study was the largest assessment of age with relation to staging of WDTC. The main limitation is its retrospective nature. Others include the relatively short average length of patient follow-up – median 5.3 years – and for those patients lost to follow-up, the causes were not known, creating potential bias. The internal validity of the study is

questionable, as differences in 10-year DSS, which were being assessed with a median follow-up of 5.3 years, could be a result of loss to follow-up, leading to selection bias.

Additionally, as the study is retrospective, there is no consistency in workup, treatment strategies, and follow-up intervals across the different institutions included. Treatment was carried out in accordance with institutional protocols, rather than by a single standardized study protocol. Depending on the initial institutional treatment, different pathways may lead to variable staging of patients. For instance, if prophylactic neck dissection was undertaken in one group of patients and more lymph nodes were sampled and found to be positive, this could lead to increased stage and stage migration.[5] Ultimately, those patients may not have been different from those who had metastatic lymph nodes which were not resected, but were assigned a different stage, and lead to bias away from the null, i.e., that the groups of patients would seem different but actually they are the same.

Another main study limitation is the inclusion dates for patients from the different institutions. While the multi-institutional nature of the study is a significant strength, including patients treated over a lengthy timeframe could lead to a significant bias. Thyroid cancer treatment has changed substantially over the last few decades and may have influenced the outcomes of the patients selected. Finally, we must note the limitations with regard to external validity and outcome bias, as all patients included were treated at high-level subspecialty care centers, and as such the study is not a true population-based study

STUDY IMPACT

Overall, patients diagnosed with WDTC have an excellent prognosis. Given that almost all patients with this diagnosis survive lengthy periods of time, it is important for clinicians to discriminate which patients are part of the majority, with lower-risk cancer, and which patients need more aggressive therapy and surveillance.

While previous studies have evaluated differential survival outcomes in WDTC patients based upon age of diagnosis, with increased age cutoffs correlating with worse prognosis by the AJCC/UICC staging system,[6,7] this study is the first multi-institutional international study to assess the impact of the proposed change in age cutoff.

The results of this study substantiated the correlation of the change in age cutoff and case downstaging. Overall, 12% of patients were downstaged, and this correlated better with patient survival outcomes. While the majority of lower-risk patients were downstaged, only a few high-risk patients (0.3% of the cohort) had a stage change. This landmark paper's high validity played an important role in the change of age cutoff to 55 years in the eighth edition of the AJCC/UICC staging system for WDTC.[8]

Downstaging those lower-risk patients will ultimately better inform clinicians about de-escalation of treatment, including less adjuvant radioactive iodine use and less extensive surgery. Furthermore, it may also decrease patient anxiety and increase the quality of life for those individuals living with WDTC.

RELEVANT ADDITIONAL STUDIES

In 2013, Bischoff et al. in a Surveillance, Epidemiology, and End Result (SEER) analysis demonstrated the lack of evidence supporting age 45 as a staging cutoff.[3] From this point, multiple studies assessed the impact of age on WDTC staging and survival outcomes. Jonklass et al. evaluated papillary thyroid cancer specifically regarding both gender and age. Their results demonstrated similar outcomes by gender overall, but also showed that outcomes differed with an age cutoff of 55 years.[9]

Mazurat et al. evaluated a cohort of 2,115 WDTC patients from the Manitoba Cancer Registry. This study found 20-year DSS to be 99% (95% confidence interval [CI] 97.9–99.6%) for patients < 45 years, 96.8% (95% CI 93.1–98.5%) for patients aged 45–54 years, 85.8% (95% CI, 78.7–90.7%) for patients aged 55–64 years, and 74.0% (95% CI, 70.0–79.8%) for those older than 65 years. On analysis, this decrease in DSS based on age was found to be statistically significant ($p = 0.002$) at age 55.[10]

The group from MSKCC in 2016 assessed the optimal age cutoff for the staging of WDTC. The group used a recursive partitioning method to assess which of the AJCC staging variables best predicted disease-specific death. Of the variables (T, N, M, and age), the presence of metastatic disease was the most powerful predictor of DSS, with age being the second most significant predictor in M0 patients. For patients with M1 disease, an age cutoff of 54 years was most predictive and an age of 56 years in patients with M0 disease.[4] Based on the recursive partitioning analysis, an age of 55 years was decided to be a better cutoff than 45 years by the MSKCC group. Overall, the change resulted in 12% of patients being downstaged and no patients being upstaged. Forty-nine percent of patients were transitioned from Stage II to Stage I, 38% of patients in Stage III were reclassified as Stage I, and 28% of patients in Stage IV were reclassified as Stage I or II. The new age cutoff improved the spread of survival across stages with 99% 10-year survival in Stage I and 74% in Stage IV as compared to 95% and 81%, respectively, with the traditional age cutoff.[4] However, even though younger patients may have improved DSS, this should not be interpreted as a correlate for risk of disease recurrence. As these analyses use survival endpoints, it should be noted that Stage I patients (under age 55 years and no metastatic disease) will have a recurrence risk that is stratified in a separate manner.[11] The analysis used here, while different from the article highlighted in this chapter, does support its overall conclusions.

This landmark paper by Nixon et al. was a clear reflection of the excellent prognosis afforded to most WDTC patients. Thyroidologists must understand the nuance in diagnosis and treatment of those diagnosed with thyroid cancer given almost none of these patients have a shortened lifespan due to their disease. Given that treatment can sometimes cause substantial morbidity, the most aggressive interventions should be saved for those individuals predicted to have a poor prognosis, when it can most significantly affect outcome. This landmark paper provides good evidence that our consideration of the age that defines lower-risk thyroid cancer should be extended to those older than previously believed.

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Chapter 22

Extent of Surgery

Review by Pavithran Maniam and Iain J. Nixon

Landmark Paper

EXTENT OF SURGERY FOR PAPILLARY THYROID CANCER IS NOT ASSOCIATED WITH SURVIVAL: AN ANALYSIS OF 61,775 PATIENTS

Adam MA, Pura J, Gu L, Dinan MA, Tyler DS, Reed SD, Scheri R, Roman SA, Sosa JA. *Ann Surg.* 2014;260(4):601–607. doi: 10.1097/SLA.0000000000000925

RESEARCH QUESTION/OBJECTIVES

Papillary thyroid cancer (PTC) represents more than 90% of all thyroid cancers and is the most indolent form of thyroid cancer, with an overall survival of greater than 90% over 20 years when appropriate treatment is given.[1,2]

For PTC larger than 1 cm in diameter, the 2009 American Thyroid Association (ATA) guidelines recommended either total or near-total thyroidectomy, and this recommendation was supported by the data presented by Bilimoria et al. in 2007.[3,4] However, more recent evidence from Mendelsohn et al. after analyzing 22,724 PTC patients (1988–2001) observed no difference in survival when comparing lobectomy and total thyroidectomy.[5] The current ATA guidelines also endorse thyroid lobectomy as adequate treatment for <4-cm, low-risk differentiated thyroid cancer (DTC) cases.[6]

Due to previous conflicting evidence, the study by Adam et al. investigated the association between the extent of surgery and overall survival after adjusting for confounding factors such as patient demographics and clinical and pathological factors.[7]

STUDY DESIGN

Retrospective cohort study of PTC patients recorded between 1998 and 2006 in the U.S. National Cancer Database (NCDB). International Classification of Diseases (ICD) codes were used to identify patients with a PTC diagnosis.

SAMPLE SIZE

In this study, 61,775 PTC patients were included.

INCLUSION/EXCLUSION CRITERIA

PTC cases measuring 1.0–4.0 cm were included. Patients younger than 18 years old, those who did not undergo surgical resection, and those with multiple cancer diagnoses

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were excluded. PTC with aggressive histological variants such as columnar, tall cell, and diffuse sclerosing variants were also excluded. The association between extent of thyroid surgery and overall survival was investigated using a Cox proportional hazard model after adjusting for variables such as demographics, comorbidities, extrathyroidal extension, radioiodine treatment, nodal disease, multifocality, and distant metastasis.[7] Analysis was restricted to patients with a minimum 5 years of follow-up. Total, complete, subtotal, and near-total thyroidectomy cases were analyzed as a total thyroidectomy. PTC patients undergoing less than a lobectomy or a surgery not specified were excluded.

INTERVENTION OR TREATMENT RECEIVED

A total of 54,926 (89%) patients underwent total thyroidectomy, and 6,849 (11%) patients underwent lobectomy.

RESULTS

The median follow-up time was 82 months (60–179 months). The total thyroidectomy group had more multifocality (29% vs. 44%), nodal disease (7% vs. 27%), extrathyroidal cancer extension (5% vs. 16%), distant metastasis (0.4% vs. 1%), positive surgical margins (7% vs. 27%), and more commonly received radioiodine treatment (33% vs. 65%) when compared to the lobectomy group. Overall survival when comparing the total thyroidectomy and lobectomy groups was similar after multivariable adjustment for patients with tumor size 1.0–4.0 cm (hazard ratio [HR] 0.96 [0.84–1.09], $p = 0.54$). Differences in overall survival remained insignificant when comparing the total thyroidectomy and lobectomy groups when stratified based on tumor size 1.0–2.0 cm (HR 1.05 [0.88–1.26], $p = 0.61$) and 2.1–4.0 cm (HR 0.89 [0.73–1.07], $p = 0.21$). Strikingly, patient factors such as older age, male gender, black race, lower income status, and comorbidity status, and tumor factors such as increasing tumor size per 0.1 cm, positive lymph node status, distant metastasis, positive surgical margin, and the absence of radioiodine treatment compromised overall survival.[7]

STUDY LIMITATIONS

All large-scale database analyses are limited by the quality of their data. The NCDB has been criticized with regards to its thyroid data, particularly in relation to previous omissions of critical data. However, the data is highly audited[8] and now includes important variables that were previously unavailable.

STUDY IMPACT

As the ATA considered updating its guidelines for publication in 2015, Adam et al. published their updated analysis of the NCDB data by including over 60,000 patients with a median follow-up of 82 months. They demonstrated no difference in survival outcome for patients with 1- to 4-cm PTC, irrespective of size. A key difference with the previous Bilimoria study was the inclusion of multifocality and extrathyroidal extension as variables in their analysis. These critical predictors of outcome had been missing from

the NCDB and other previous analyses at the time of publication in 2008. Inclusion of these variables, among others in the multivariable analysis, refined the results of previous analyses and confirmed that, for low-risk disease, no significant difference in survival could be demonstrated, even when a huge cohort of patients was included across multiple institutions. These findings influenced the ATA guidelines, which subsequently moved away from recommending total thyroidectomy for patients with low-risk thyroid cancers.

The impact of these findings was compounded by the fact that they were published at a time when a massive rise in the incidence of thyroid cancer was being seen not only in the United States but also internationally.[9–11] Importantly, this increase has been most marked for low-volume, low-risk thyroid cancers.[12] Therefore, an increasing number of patients were now considered potential candidates for less than total thyroidectomy worldwide.

This is critical, as it has now been convincingly shown that increased extent of thyroid surgery is associated with an increased risk of complications, regardless of the volume of procedures performed by a surgeon.[13] This means that patients managed with total thyroidectomy, as opposed to thyroid lobectomy, are more likely to suffer injury to their recurrent laryngeal nerve(s), hypocalcemia, and require lifelong thyroid hormone replacement.

The influence of the paper by Adam et al. on the ATA guidelines came at a time when more patients were undergoing thyroid surgery, and therefore had the potential to have an impact on thousands of patients in the United States and beyond. This conservative approach to treatment was supported by the updated 2015 iteration of the ATA guidelines,[6] which endorsed thyroid lobectomy as adequate treatment for <4 cm low-risk DTC. In response to these changes, and as one would expect, rates of total thyroidectomy are now falling.[14]

RELEVANT ADDITIONAL STUDIES

The extent of primary surgery required for treatment of DTC has been, and remains, a controversial topic that has dominated debate for decades. The recognition that DTCs have excellent outcomes in the early 20th century presented an academic challenge to researchers, as the event rate in this group of patients was low. Few patients recurred, and almost no patients died of their disease. Therefore, large cohorts were required to analyze outcomes in a meaningful way. The first group to achieve this was Mazzaferri et al. from Ohio State, USA, in 1977.[15] This group analyzed the U.S. Air Force database and showed that a more aggressive approach to surgery (i.e., total thyroidectomy) coupled with radioactive iodine was associated with improved rates of survival and recurrence. This study was limited by small sample size, a lack of risk stratification (which had yet to be developed), and a cohort that predated the routine use of ultrasound and fine needle aspiration biopsy. Despite its limitations, this publication shaped the international approach to the management of well-differentiated thyroid cancer for years to come. Clinicians had evidence to base decisions on oncological outcomes, and practice standardized around the principle that almost all patients with DTC should undergo total thyroidectomy with postoperative adjuvant radioactive iodine.

The paper by Mazzaferri et al. remained relevant for years, and the evidence was cited in major guidelines, including the ATA guidelines in 2009.[3] That iteration of the influential document was published shortly after Bilimoria et al. presented an analysis of over 40,000 PTC patients from the NCDB,[16] which again confirmed the finding that total thyroidectomy was superior to thyroid lobectomy in terms of oncological outcomes. Therefore, with significant supporting evidence of international guideline endorsement, total thyroidectomy became the international standard of care for DTC patients.

However, not all groups agreed with this consensus. During the late 20th century, several institutions analyzed their practice and highlighted that, with contemporary risk stratification, low-risk patients, who constitute the majority of patients with DTC, could safely be managed with thyroid lobectomy alone.[17–19] In addition, the authors also highlighted the weaknesses of the Mazzaferri and Bilimoria data.[20,21] However, these groups' data were limited to single institutional experiences with small patient cohort sizes, raising the question of whether such an approach was applicable outside of the major centers of excellence, which had been able to accrue such long-term data.

Despite the recognition that low-risk thyroid cancers can now be treated with thyroid lobectomy rather than total thyroidectomy in the majority of cases, there remain unanswered questions. Despite equitable survival rates, recurrence may be more common following thyroid lobectomy, particularly with regard to the development of contralateral lobar disease. Therefore, the ideal frequency, duration, and method of follow-up remain unclear. Previously, patients who underwent total thyroidectomy with postoperative radioactive iodine treatment were candidates for accurate follow-up with serial thyroglobulin assessments. However, such biochemical surveillance is less reliable in patients who have a residual thyroid lobe.[22]

In addition, the extension of the concept of conservative treatment for thyroid cancer has led to some units actively surveilling patients with low-risk thyroid cancers.[23,24] Such an approach is gaining popularity in Japan and the United States, given the recognition that overdiagnosis is a significant problem in thyroid cancer. In well-selected cases, this approach has the benefit of eliminating iatrogenic injury, as the vast majority patients do not convert to surgery during the follow-up period. Although previously limited to <1-cm tumors, experience with managing larger tumors is now growing.[25]

In conclusion, the paper by Adam et al. came at a time when a growing number of patients with low-risk thyroid cancer were being overtreated. By recognizing the limitations of previous studies and refining their analysis based on the improved NCDB, this group was able to provide the critical evidence base required to support a less aggressive approach to the management of thyroid cancer for an increasing number of patients worldwide. This work provides a platform for further research into identification of patients suitable for active surveillance and an approach to follow-up that balances patients' risk with available healthcare resources.

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CHAPTER 23

Central Neck Dissection

Review by Shayanne A. Lajud and Jeremy L. Freeman

Landmark Paper

HOW MANY LYMPH NODES ARE ENOUGH? ASSESSING THE ADEQUACY OF LYMPH NODE YIELD FOR PAPILLARY THYROID CANCER

Robinson TJ, Timothy J., Samantha Thomas, Michaela A. Dinan, Sanziana Roman, Julie Ann Sosa, and Terry Hyslop. *J Clin Oncol*. 2016;34(28):3434–3439. doi: 10.1200/JCO.2016.67.6437

RESEARCH QUESTION/OBJECTIVES

Papillary thyroid carcinoma (PTC) is the most common type of thyroid cancer. The central neck compartment is frequently involved, with up to 35% of patients presenting with N1 disease. In addition, it has been estimated that up to 80% of patients presenting with clinically N0 (cN0) disease may harbor microscopic lymph node (LN) metastasis to the central compartment (levels VI and VII). According to the American Head and Neck Society, a central neck dissection (CND) involves a comprehensive removal of pretracheal, prelaryngeal, and at least one paratracheal nodal basin.[1] While a CND is recommended for N1 disease, it may increase the risk of postoperative hypoparathyroidism and recurrent laryngeal nerve (RLN) injury.[2] The role of prophylactic CND (pCND) in the setting of cN0 disease is less clear.[3] However, in experienced hands it may provide more accurate staging information, as well as potentially improving locoregional control, without significantly increasing morbidity.[3,4] The selected landmark paper seeks to establish the adequacy of nodal yield to better estimate the risk of occult nodal disease using probability statistics from a large retrospective PTC patient cohort.

STUDY DESIGN

This was a retrospective analysis of data from the National Cancer Database (1998–2012) to assess the nodal positivity distribution by T-stage among adult patients diagnosed with ≥1 cm PTCs who underwent thyroidectomy with one or more LNs surgically examined, and no evidence of distant metastatic disease identified at diagnosis.

SAMPLE SIZE

Data from 78,724 adult PTC patients was analyzed.

INCLUSION/EXCLUSION CRITERIA

Adult patients with a diagnosis of PTC with tumor size ≥1 cm, no distant metastases, and who had undergone surgery were included. Patients with either an unknown

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number of LNs or no LNs examined, or with an unknown number of positive LNs, were excluded.

INTERVENTION OR TREATMENT RECEIVED

A β-binomial distribution was used to estimate the risk of occult LN involvement as a function of LNs examined and pathologic T-stage.

RESULTS

A total of 38,653 (49.1%) patients were observed to have metastatic nodal disease. Factors associated with nodal metastases included advanced T-stage, extrathyroidal cancer extension, positive margins, and male sex. Patients with nodal disease (N+) were more likely to receive radioactive iodine (RAI) treatment compared to those without nodal disease (N0) (69.6% vs. 58.3%; $p < 0.001$).

The probability of a false-negative LN dissection was estimated to be 53% when a single LN was examined. This probability decreased from 53% to 11% as the number of LNs examined increased from one to six LNs (step 1). The observed prevalence was 49.1%, and the overall true prevalence of N+ disease (observed + false negative) was estimated to be 62.1%. The observed true prevalence increased as a function of increased T-stage (T1b 47%–98.4%), and after accounting for false negatives this increased from 47.1% to 98.4% (step 2). The risk of occult disease was calculated in step 3, and from this it was calculated that a total of 6, 9, and 18 nodes needed to be examined in patients with pT1b, pT2, and pT3 disease, respectively, to confidently rule out the presence of occult nodal disease. When limited to central compartment LNs, a total of three, four, or eight LNs needed to be examined to rule out occult disease for pT1b, pT2, and pT3 stages, respectively.

The quartile of occult nodal disease risk was significantly associated with 10-year overall survival (OS). A higher probability of occult nodal disease was associated with the lower OS (93% in the highest quartile probability group compared with 96%–97% in the remaining quartiles).

STUDY LIMITATIONS

The study is limited by its retrospective nature and the accuracy of the dataset. Additionally, the cohort used in the initial modeling was derived from patients who had at least two lymph nodes examined, potentially overestimating the risk of residual disease.

STUDY IMPACT

This article is considered a landmark paper because it helps estimate the risk of occult nodal disease in PTC patients based on the T-stage and number of LNs evaluated. In general, the higher the T-stage, the greater number of LNs that need to be removed and evaluated to confidently rule out occult disease. Importantly, it helps standardize the interpretation of pCND by understanding the adequacy of the dissection based on T-stage.

RELEVANT ADDITIONAL STUDIES

The role of prophylactic central compartment LN dissection is a highly controversial topic with reasonable clinical arguments from both sides.[5] Advocates for pCND argue that it improves the accuracy of pathological staging, likelihood of postoperative a thyroglobulinemia, and reduces the need for reoperations. Arguments against pCND include a greater risk of hypoparathyroidism and recurrent laryngeal injury, without a reduction in the risk of clinical recurrence or mortality. Unfortunately, the current literature is primarily limited to retrospective studies, thus making it difficult to draw strong conclusions.

A large retrospective, multicenter, cohort study found that pCND was associated with lower thyroglobulin (Tg) levels and reduced need for reoperation with in the central compartment.[6] More specifically, the group of patients who underwent total thyroidectomy (TT) with pCND in this study had less than half the level of stimulated Tg compared with the group who underwent TT alone (6.6 vs. 15.5 ng/mL, $p = 0.025$). Similarly, the addition of pCND led to fewer reoperations (1.5 vs. 6.1%, $p = 0.04$). Another large retrospective study demonstrated that bilateral pCND followed by personalized RAI therapy improved both 10-year disease-specific survival (98% vs. 92.5%, $p = 0.034$) and locoregional control (94.5 vs. 87.6%, $p = 0.003$), without increasing the risk of permanent morbidity.[4] Notably, pCND was found to be an independent predictive factor for improved locoregional control at 10 years after surgery (odds ratio 0.21, 0.11–0.41, $p < 0.001$). However, there was no significant difference in the rates of permanent hypoparathyroidism (HPT) and RLN injury when comparing the groups (TT with pCND vs. TT alone).

Unilateral pCND has also been advocated. The rationale for this approach is that the incidence of contralateral paratracheal LN metastases in cN0 patients is low. The advantage of unilateral pCND compared to bilateral pCND is lower incidence of postoperative HPT, without compromising postoperative Tg levels or RAI uptake; in addition, the contralateral RLN is not subject to the added risk of injury from LN dissection.[7]

A systematic review and meta-analysis from 2013 that compared TT with or without pCND for PTC found a decreased risk of locoregional recurrence, with an increased risk of temporary hypocalcemia and overall morbidity in the pCND group.[3] However, a more recent systematic review and meta-analysis of the available five randomized controlled trials (RCTs), which included 795 patients, showed no significant difference between these two groups in terms of both locoregional control and postoperative morbidity.[8]

While the aforementioned studies suggest a possible oncological advantage for performing pCND in addition to thyroidectomy, most authors support the notion that it may lead to higher complication rates.[9] In particular, the rate of transient RLN injury and HPT ranges from 0% to 7.3% and from 8.7% to 85%, respectively. Similarly, the rate of permanent RLN injury and HPT ranges from 0% to 5.9% and from 0% to 16.2%, respectively.

It is important to note that a recent analysis of available systematic reviews on this topic found that the quality of their methodology was critically low, with only a third of reviews adhering to methodological guidelines.[10] Therefore, the results of these studies should be interpreted with caution.

Unfortunately, performance of a large prospective RCT evaluating pCND in cN0 patients was determined to be impracticable given the low rates of newly identified structural disease and morbidity after surgery for cN0 PTC.[5] Therefore, it is imperative that the clinician individualize care based on their patients' risks and audit their own complication rates to better counsel the patient on how to best treat the disease. Currently the American Thyroid Association recommends that pCND (unilateral or bilateral) should be considered in patients who are cN0 and have advanced primary tumors (T3 or T4) or clinically involved lateral neck nodes, or if information gained from pCND would be used to plan further treatment, though the strength of this recommendation was rated as being weak and the quality of the evidence base as low.[2]

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Chapter 24

Recurrent Differentiated Carcinoma

Review by Agamemnon Pericleous, Samuel Backman, Matilda Annebäck, and Neil Tolley

Landmark Paper

ESTIMATING RISK OF RECURRENCE IN DIFFERENTIATED THYROID CANCER AFTER TOTAL THYROIDECTOMY AND RADIOACTIVE IODINE REMNANT ABLATION: USING RESPONSE TO THERAPY VARIABLES TO MODIFY THE INITIAL RISK ESTIMATES PREDICTED BY THE NEW AMERICAN THYROID ASSOCIATION STAGING SYSTEM

Tuttle RM, Tala H, Shah J, Leboeuf R, Ghossein R, Gonen M, Brokhin M, Omry G, Fagin JA, Shaha A. *Thyroid*. 2010;20(12):1341–1349. doi: 10.1089/thy.2010.0178

RESEARCH QUESTION/OBJECTIVES

The 2009 American Thyroid Association (ATA) revised guidelines[1] conclude that the American Joint Commission on Cancer (AJCC) staging system[2] does not include all parameters relevant for differentiated thyroid cancer (DTC). Moreover, the AJCC staging system is primarily designed to predict risk of death rather than risk of persistent/recurrent disease. A novel risk-stratification system designed specifically to predict outcomes relevant to DTC was proposed, and it was stated that ongoing risk assessment is required for appropriate management. This landmark paper aims to validate the ATA staging system for predicting risk of recurrent/persistent disease and determine if assessment of response to therapy during the first 2 years after treatment can modify the initial risk estimates. The authors propose a new risk stratification scheme, incorporating the response to therapy, to refine the initial risk assessment built on the ATA staging system.

STUDY DESIGN

This is a retrospective study of patients followed for a median of 7 (range 1–15) years after total thyroidectomy and radioactive iodine remnant ablation for treatment of DTC at Memorial Sloane Kettering Cancer Center (MSKCC).

SAMPLE SIZE

A total of 710 consecutive DTC patients were assessed for study eligibility, out of which 588 patients were included. Out of these, 471 patients could be assessed for their response to therapy.

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INCLUSION/EXCLUSION CRITERIA

The patients must have undergone total thyroidectomy and radioactive iodine remnant ablation between January 1994 and December 2004, either at the study center or elsewhere. Moreover, a follow-up ultrasound must have been performed at MSKCC and clinical information had to be available.

Patients were excluded if there was inadequate follow-up information, evidence of interfering anti-thyroglobulin (Tg) antibodies, or insufficient clinical information for initial staging. Moreover, patients younger than 18 years at age of diagnosis, as well as patients with anaplastic thyroid cancer present on histology, were excluded. A minimum of 3 years follow-up was required, unless one of the clinical end points (death or recurrence) was reached before that time point.

INTERVENTION OR TREATMENT RECEIVED

The patients were classified based on ATA criteria as having either low, intermediate, or high risk of recurrent/persistent disease. Their response to therapy was classified as either being excellent, acceptable, or incomplete based on clinical data from the first 2 years of follow-up. Each patient was also staged according to the AJCC staging system. The clinical outcomes of these groups were assessed.

Initial Risk Stratification Criteria

Patients were classified as having low-risk disease if there were no local or distant metastases, complete macroscopic resection, no invasion of locoregional tissues, no aggressive histology, no vascular invasion, and no ^{131}I uptake outside the thyroid bed on posttreatment scintigraphy. Intermediate-risk disease was diagnosed when there was microscopic invasion of perithyroidal soft tissues, cervical lymph node metastases, ^{131}I uptake outside of the thyroid bed, or aggressive histology or vascular invasion present in pathology. High-risk disease required the presence of either distant metastases, gross residual disease after resection, or macroscopic invasion.

Classification of Response to Therapy

Excellent response required suppressed and stimulated Tg < 1 ng/mL as well as no evidence of disease on neck ultrasound or cross-sectional imaging or scintigraphy. If there was suppressed Tg < 1 ng/mL but stimulated Tg in the range 1–10 ng/mL, or neck ultrasound with nonspecific changes or stable lymph nodes smaller than 1 cm, or nonspecific changes on cross-sectional/nuclear medicine imaging, the response was classified as acceptable. The response was classified as incomplete if the suppressed Tg was 1 ng/mL or greater, the stimulated Tg was 10 ng/mL or greater, if the Tg values were rising, or if there was persistent or recurrent structural disease on imaging.

RESULTS

The AJCC staging system did not reliably predict the risk of persistent or recurrent disease, although the probability of having no evidence of disease (NED) at the end of

follow-up was lower for patients with AJCC stage IV disease. This group was also more likely to have persistent structural disease and included most patients who died from thyroid cancer.

The ATA staging system performed better; patients in the low-risk group had an 86% probability of having NED during follow-up, while patients in the intermediate- and high-risk groups had probabilities of having NED of 57% and 14%, respectively. The risk of having persistent, structurally identifiable disease was 2%, 19%, and 67% in the low-, intermediate-, and high-risk groups, respectively. Notably, all patients who died from thyroid cancer belonged to the high-risk group.

When restratified based on response to therapy, 96% of the excellent responders, 87% of the acceptable responders, and 4% of the incomplete responders did not have evidence of disease during follow-up. Persistent structurally identifiable disease was found in 57% of the patients with an incomplete response and in 0% of those with an acceptable or excellent response to therapy.

The largest utility of restratification based on response to therapy appears in the intermediate- and high-risk groups, where an excellent response to therapy drastically reduces the risk of persistent or recurrent disease, while an incomplete response is associated with a significantly increased risk.

STUDY LIMITATIONS

The study is a retrospective single-center study, meaning that there could be bias both in the inclusion (e.g., some patients had their primary treatment elsewhere but sought follow-up at the study center) and because patients were lost to follow-up and could not be included. Moreover, the median follow-up of 7 years may not be sufficient in the context of DTC; some patients may have been alive with no evidence of disease at the end of the follow-up period but developed recurrent disease later, as DTC recurrences may occur many years after initial treatment.[3]

STUDY IMPACT

The landmark paper validates the ATA risk stratification system as a tool for the first years after initial treatment, and provides a template for how ongoing risk assessment can be carried out. Moreover, the article provides evidence that risk assessment in the years after initial treatment provides additional predictive power to identify patients at risk of developing recurrent or persistent disease compared to staging at initial treatment alone. These findings contributed to revisions made in the 2015 ATA guidelines.[4]

RELEVANT ADDITIONAL STUDIES

Several additional articles have similarly validated the ATA staging system and the utility of re-stratification after initial treatment. Pitoia et al. applied both the ATA criteria and the Latin American Thyroid Society Risk of Recurrence Classification

System (LATS) in a cohort of 171 thyroid cancer patients and validated the utility of these systems in predicting the occurrence of both persistent structural and recurrent disease.[5] Vaisman et al.[6] applied the ATA staging criteria and the MSKCC response to therapy criteria to a Brazilian cohort of 506 patients and validated the ability of response to therapy to predict risk of persistent/recurrent disease. Interestingly, in this article a significant proportion of patients with an acceptable response to therapy, as well as a proportion of those with incomplete biochemical response to treatment, were eventually classified as having NED, without additional therapy. Castagna et al.[7] applied the ATA criteria and a system similar to the MSKCC criteria based on biochemistry (basal and stimulated Tg, anti-Tg antibodies), clinical examination, and radiology (neck ultrasound and in some cases ^{131}I-scintigraphy) to reclassify patients 8–12 months after their initial treatment and found an increased predictive power compared with only staging at initial treatment.

The proposed system for assessing response to therapy includes measuring Tg following stimulation by recombinant thyrotropin, as well as measuring basal (suppressed) Tg. While stimulated Tg is a more sensitive test for detecting residual tumor tissue, it is a more resource-intensive test and may not be cost-effective in all healthcare systems. First, as demonstrated by Vaisman et al., patients with detectable Tg without structural disease are often eventually rendered NED without additional therapy, indicating that an incomplete biochemical response without evidence of structural disease may not always be clinically relevant.[6] Second, modern Tg assays are increasingly sensitive, which may decrease the utility of thyrotropin stimulation. It has been suggested that basal Tg measured with a modern highly sensitive assay should be sufficient for the monitoring of most patients.[8] A recent randomized controlled trial that included 196 patients suggested that a highly sensitive Tg assay may eliminate the need for stimulated Tg measurement in a subset of patients, specifically those with suppressed Tg levels below 0.1 ng/mL.[9] The choice of follow-up studies for DTC should consider both the benefit to the patients and the prudent use of healthcare resources. Future work may also include prognostic molecular markers to further refine thyroid cancer risk stratification.

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Chapter 25

Recombinant TSH/Adjuvant Radioactive Iodine Therapy

Review by Daegan Sit, Jonn Wu, and Sarah Hamilton

Landmark Paper

RECURRENCE AFTER LOW-DOSE RADIOIODINE ABLATION AND RECOMBINANT HUMAN THYROID-STIMULATING HORMONE FOR DIFFERENTIATED THYROID CANCER (HiLo): LONG-TERM RESULTS OF AN OPEN-LABEL, NON-INFERIORITY RANDOMISED CONTROLLED TRIAL

Dehbi HM, Mallick U, Wadsley J, Newbold K, Harmer C, Hackshaw A. *Lancet Diabetes Endocrinol.* 2019 Jan;7(1):44–51. doi: 10.1016/S2213-8587(18)30306-1. Epub 2018 Nov 27.

RESEARCH QUESTION/OBJECTIVE

The HiLo study was a noninferiority phase 3 study of well-differentiated thyroid cancer (WDTC) patients treated with one-stage or two-stage total thyroidectomy that compared ablation strategies with high-dose (3.7 GBq) versus low-dose (1.1Gbq) radioactive iodine ^{131}I (RAI), and thyrotropin stimulation with either recombinant human thyrotropin (rhTSH) or thyroid-hormone withdrawal in a four-arm, factorial design. The primary end point was rates of thyroid ablation at 6–9 months. The landmark paper chosen for this chapter was a follow-up study of patients from the HiLo trial to determine if disease recurrence rates differed between patients receiving low versus high-dose RAI.

The primary study end point was the success rate for ablation, which was defined as both a negative scan (<0.1% uptake on the basis of the region-of-interest method drawn over the thyroid bed) and a thyroglobulin level of less than 2.0 ng/mL at 6–9 months follow up.

STUDY DESIGN

The HiLo study was an open-label, noninferiority randomized control trial conducted at 29 centers in the UK. All patients underwent a total thyroidectomy, with lymph node dissection if there was evidence of nodal metastases or if it was institutional practice. Each patient in the trial was randomized to one of four treatment strategies, in a factorial design, and received one of two methods of thyrotropin stimulation – administration of rhTSH or thyroid-hormone withdrawal – and one of two ^{131}I activities (1.1 GBq or 3.7 GBq).

The original publication of the HiLo trial reported the primary end point of thyroid ablation at 6–9 months after RAI administration. This was assessed with the use of neck

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ultrasonography and determination of the level of rhTSH-stimulated serum thyroglobulin (≤1 ng/mL) or a diagnostic ^{131}I total-body scan with 148–185 MBq in patients with detectable antithyroglobulin antibody.[1] Our chosen landmark article examined the prespecified secondary end point of the HiLo trial of disease recurrence.

The primary study end point was the rate of disease recurrence in patients receiving low-dose versus high-dose RAI. There was no standard follow-up surveillance for recurrence which was diagnosed according to national (UK) standards using serum thyroglobulin and thyroglobulin antibody measurements, ultrasound, fine needle aspiration cytology, RAI scans, PET-CT scans, and MRI, as applicable. For confirmation of recurrence, all underwent either fine needle aspiration or sensitive imaging (PET-CT or RAI scans). The outcome was defined as the time from randomization to first recurrence or death, with hazard ratios (HRs) obtained from Cox proportional hazards regressions. Patients without recurrence were censored at their last follow-up visit. The authors retrospectively performed a noninferiority calculation, based on the following: 1) a noninferiority margin of 5 percentage points for the difference in proportion of recurrence and 2) a noninferiority HR of 2.05 corresponding to an expected recurrence-free rate of 95% for the high-dose and 90% for the low-dose arm.

SAMPLE SIZE

A total of 438 patients were recruited between January 16, 2007, and July 1, 2010. The sample size calculation was based on the desired noninferiority calculation for the HiLo study's primary end point of ablation success.[1]

INCLUSION/EXCLUSION CRITERIA

Inclusion criteria:

- Aged 16–80 years
- Eastern Cooperative Oncology Group performance status of 0–2
- Histological confirmation of differentiated thyroid cancer requiring RAI ablation
- Tumor T stage T1–T3 (TNM, 6th edition)
- Lymph node involvement permitted (N0, NX, and N1)
- One-stage or two-stage total thyroidectomy permitted with or without prophylactic central compartment lymph node dissection

Exclusion criteria:

- No distant metastasis (M0)
- No microscopic residual disease
- Presence of aggressive malignant variants
- Anaplastic or medullary carcinoma
- Pregnancy
- Severe coexisting conditions

- Previous cancer with limited life expectancy
- Previous ^{131}I or ^{123}I preablation scanning
- Previous treatment for thyroid cancer except for surgery

Stratification variables were center, T-stage, and N-stage.

INTERVENTION OR TREATMENTS RECEIVED

Patients were randomly assigned to low-dose (1.1 GBq) or high-dose (3.7 GBq) RAI remnant ablation, each with either rhTSH (thyrotropin alfa [Sanofi, Bridgewater New Jersey, USA]) or thyroid hormone withdrawal, in a 1:1:1:1 randomization ratio. Randomization was stratified for center, tumor stage, and nodal stage and was conducted centrally.

RESULTS

The number of patients by treatment group included 110 assigned to 1.1 GBq with rhTSH, 110 assigned to 1.1 GBq with thyroid hormone withdrawal, 109 assigned to 3.7 GBq with rhTSH, and 109 assigned to 3.7 GBq with thyroid hormone withdrawal. Patients included in this study corresponded to American Thyroid Association (ATA) 2015 classification system low-risk patients (T1–T2, N0) and select intermediate-risk patients (T3 or N1a/b). Baseline characteristics, including T-stage and N-stage, were similar between groups. By December 31, 2017, follow-up data was available for 434 patients. Four patients were lost to follow-up: three from the 1.1 GBq with thyroid withdrawal group and one from the 3.7 GBq rhTSH group. Median study patient follow-up was 6.5 years (interquartile range [IQR] 4.5–7.6 years).

There were a total of 21 recurrences, with 11 reported in the low-dose group and 10 reported in the high-dose group. Four patients (two in each dose group) were found to actually have persistent disease but were included as recurrence for the purposes of analysis. Cumulative recurrence rates were similar between low-dose and high-dose RAI groups (3 years, 1.5% vs. 2.1%; 5 years, 2.1% vs. 2.7%; and 7 years, 5.9% vs. 7.3%; hazard ratio [HR] 1.10, 95% confidence interval [CI] 0.47–2.59, $p = 0.83$).

The statistical test for noninferiority to exclude a 5 percentage-point difference was significant ($p_{noninferiority} = 0.01$). However, the other statistical test for noninferiority to exclude an HR of 2.05 was not statistically significant between arms ($p_{noninferiority} = 0.08$). Thus, based on the second statistical test, the authors could not claim noninferiority between the two treatment arms.

STUDY LIMITATIONS

This study reported long-term data that remnant ablation with a higher or lower dose of RAI was not associated with a difference in disease recurrence, in line with the ESTAMBL trial (outcome after ablation in patients with low-risk thyroid cancer), which asked a similar question.[2,3] A limitation of the study design of the HiLo trial

was that the primary outcome was rate of ablation, and thus the patient accrual numbers and follow-up design were not based on expected rates of disease recurrence. Moreover, while disease recurrence was a prespecified secondary outcome, the two noninferiority tests were defined post hoc. Only one of the two noninferiority tests were statistically significant, and the authors were not able to exclude an HR of 2.05 for the low-dose RAI arm ($p_{noninferiority} = 0.08$). The authors do note that the *p*-value of 0.08 was a borderline result for noninferiority,[4] and ultimately, the low absolute numbers of recurrences were similar in each arm (11 who had 1.1 GBq ablation and 10 who had 3.7 GBq ablation).[4]

Ascertaining successful ablation did not depend on neck ultrasound, as this "was not routinely used in the UK at the time of the trial as part of the 6–9-month assessment after ablation." Thus, it was not possible to distinguish whether a patient had a structural complete response (and was therefore disease-free) or had actual persistent disease.

Another study limitation was that there was no standard follow-up schedule. The reasoning provided was that it would have added substantial cost to the study. While note was made that recurrences were diagnosed "according to national standards," the follow-up schedule, including laboratory testing schedules, was not expanded upon; these could have implications on treatment and reliable, accurate follow-up. For instance, not monitoring closely for thyroid-stimulating hormone (TSH) suppression could lead to higher risks of cancer recurrence.

Finally, while a substantial number of intermediate-risk patients were accrued, they ultimately comprised a minority of study participants (147 of 438 patients accrued). Among these patients, the rate of recurrences were 7.1% in the low-dose group versus 9.1% in the high-risk group ($p = 0.67$).

STUDY IMPACT

The results of the HiLo study are encouraging for treatment de-escalation to lower doses of RAI for low-risk WDTC patients, allowing for lower total body doses of irradiation and lower rates of toxicity, particularly lacrimal complications.[3] This study also demonstrated that patients had similar rates of recurrence whether they had iodine withdrawal versus exogenous Thyrogen. This is important for patients and providers, as iodine withdrawal is associated with higher rates of symptoms including fatigue, difficulty concentrating, sleep disturbances, constipation, and difficulty performing usual activities at work.[1–3] This study's median follow-up at 6.2 years provides useful data on the time to recurrence, demonstrating that most recurrences occur after 5 years and highlights the importance of continued surveillance follow-up beyond this period.

RELEVANT ADDITIONAL STUDIES

The ESTIMABL1 trial was a phase 3 equivalence study that also studied thyroid ablation strategies, following complete thyroidectomy for exclusively low-risk WDTC.[2,3] Similar to the HiLo trial, a factorial 1:1:1:1 design was used, testing RAI ablation

with low-activity (1.1 GBq) versus high-activity (3.7 GBq) and two strategies of TSH stimulation with rhTSH versus iodine suppression. Equivalence was shown for the primary outcome of thyroid ablation at 6–10 months between low-activity and high-activity RAI and also between the use of rhTSH injections and thyroid hormone withdrawal. No difference in disease recurrence was observed with a median follow-up; however, median follow-up time was shorter than the HiLo trial at 5.4 years (range 0.5–9.2). Freedom from disease recurrence was 98% for this study cohort. In addition, unlike the HiLo trial, the ESTAMBL1 study only included low-risk patients. Overall, the concordant results of the ESTIMABL1 trial gives reassurance that ablation of low-risk WDTC patients with rhTSH and 1.1 GBq is safe; however, intermediate-risk patients were not eligible for inclusion in this trial.

The ATA guidelines provide recommendations on the use of RAI for remnant ablation (to facilitate detection of recurrent disease and initial staging by tests such as thyroglobulin measurements or whole-body RAI scans), adjuvant therapy (in the case of microscopic disease), or therapy (in the case of persistent disease).[5] Due to the lack of prospective data, these recommendations are based on large retrospective series.[6–8] The ATA does not recommend routine ablation for low-risk patients, but consideration for cases with aggressive features, noting the lack of data supporting a survival benefit in this patient population.[6,7] RAI can be considered for patients with T1b-T2, N0/NX, M0 WDTC *with* aggressive histology or vascular invasion. RAI should be considered for patients with low- to intermediate-risk WDTC who have T3N0M0 disease and is favored for patients with T1-3 N1a/N1b M0 WDTC.

Schvartz et al. published their retrospective registry study of 1,298 ATA low-risk patients with a median 10.3 years of follow-up. They did not find that RAI significantly improved disease-free survival or overall survival.[7] Long-term patient outcomes were very good, with 10-year overall survival (OS) rates of 95.8% for patients who did not receive RAI and 94.6% for patients who received RAI. Meanwhile, the 10-year disease-free survival (DFS) rates were 93.1% for patients not treated with RAI and 88.7% for patients treated with RAI. These differences in OS and DFS were not statistically significant on multivariable analysis or propensity score analysis.

The National Thyroid Cancer Treatment Cooperative Study Group conducted a prospective multicenter registry study of 2,936 WDTC patients.[9,10] They found no disease recurrence or disease-specific survival benefit for RAI in patients <45 years with no distant metastases or patients aged ≥45 years with a primary tumor <4 cm in diameter, no extrathyroidal extension, and no nodal metastases. They did, however, find a disease-specific survival benefit for WDTC with extrathyroidal extension, lymph node involvement, metastatic disease, or in patients aged ≥45 with a tumor size larger than 4 cm.

Whether RAI ablation could be avoided altogether for the treatment of low-risk WDTC is the next question in de-escalation, and this is further investigated in the Iodine or Not (IoN) trial for low- and intermediate-risk patients and ESTIMABL2 for low-risk patients (ESTIMABL2, NCT01837745; IoN, NCT01398085).

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Chapter 26

Targeted Therapy

Review by Arif Adnan Shaukat

Landmark Paper

SORAFENIB IN RADIOACTIVE IODINE-REFRACTORY, LOCALLY ADVANCED OR METASTATIC DIFFERENTIATED THYROID CANCER: A RANDOMISED, DOUBLE-BLIND, PHASE 3 TRIAL

Brose MS, Nutting CM, Jarzab B, Elisei R, Siena S, Bastholt L, Fouchardiere C, Pacini F, Paschke R, Shong YK, Sherman SI, Smit JWA, et al. *Lancet.* 2014;384(9940):319–328. doi: 10.1016/S0140-6736(14)60421-9

RESEARCH QUESTION/OBJECTIVES

Thyroid cancer is a global disease that carries a high cure rate. The incidence of thyroid cancer (papillary thyroid cancer mainly) has been increasing steadily in both sexes.[1] Despite the noted increase in incidence, there has been a noted decline in thyroid cancer mortality.[2] The mainstay of curative treatment for differentiated thyroid cancer (DTC) remains surgery, radioiodine, and *l*-thyroxine therapy.[3] However, between 7% and 23% of patients will eventually develop treatment-refractory disease.[4,5] These patients pose a challenge due to a lack of effective treatment options.[6] Lack of effective chemotherapeutic and radiotherapy options led to research that aimed to identify biological targets for treatment of this cancer. Several genetic alterations, such as *RET/PTC* translocations and *BRAF* point mutations in DTC have been identified.[7] More significant is the identification of vascular endothelial growth factor (VEGF) and its receptor (VEGFR) as a treatment target.[8] Sorafenib (Nexavar®, Bayer, Leverkusen, Germany) (a VEGFR inhibitor) has been studied in phase 2 trials and was found to demonstrate efficacy for treatment of refractory thyroid cancer cases. This led to the development of the DECISION trial (stuDy of sorafEnib in loCally advanced or metastatIc patientS with radioactive Iodine refractory thyrOid caNcer).[9]

STUDY DESIGN

A multicenter randomized, double-blind placebo-controlled phase 3 trial of sorafenib for treatment of locally advanced or metastatic differentiated thyroid cancer.

SAMPLE SIZE

Four hundred and seventeen patients from 77 centers in 18 countries were randomized.

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INCLUSION/EXCLUSION CRITERIA

Patients with papillary, follicular (including Hurthle cell variant), and poorly differentiated thyroid cancer with full thyroid-stimulating hormone (TSH) suppression (TSH < 0.5 IU/L) were included; 96.4% of the patients randomized had metastases to lung, bone, or lymph nodes. Radioactive iodine (RAI)–refractory disease was defined as 1) the presence of one or more target lesions without iodine uptake or 2) patients whose tumors had iodine uptake and a) progressed after one RAI treatment within the past 16 months; b) progressed after two RAI treatments within 16 months of each other, with the last RAI treatment administered >16 months earlier; or c) received cumulative RAI activity ≥22.3 GBq (≥600 mCi). Patients who had received chemotherapy or thalidomide therapy were excluded.

INTERVENTION OR TREATMENT RECEIVED

Patients received sorafenib in the active arm versus placebo. The primary end point of the study was progression-free survival (PFS). Patients in the placebo arm were allowed to cross over to sorafenib, open label, upon progression. The secondary study end points were overall survival (OS), time to progression (TTP), and objective response rate (ORR).

Exploratory biomarker analyses were also carried out to identify potential predictive, prognostic, or pharmacodynamic biomarker candidates as part of this study. The statistical analysis was based on assuming one-sided alpha 0.01, 90% power, and 55.5% improvement in PFS requiring 267 progression-free events from 420 patients. All tests were stratified by age (younger or older than 60 years) and geographical region (North America vs. Europe vs. Asia). Cox proportional hazard model analysis was used to calculate confidence intervals (CIs) and hazard ratios (HRs).

RESULTS

The study was opened for recruitment from September 2009 to August 2011. The primary end point of PFS was met showing significant improvement for sorafenib compared with placebo (HR, 0.59; 95% CI, 0.45–0.76; $p < 0.0001$; median 10.8 vs. 5.8 months, respectively) with a 41% reduction in the risk of progression or death during the double-blind period. Improvement in PFS was noted in all prespecified subgroups, including age, sex, geographical region, histology, sites of metastases, and tumor burden. There was no significant difference in OS noted within the specified period. Median OS had not been reached at the time of reporting of the trial.

A partial response was noted in 12.2% of the patients (0.5% placebo arm). Median duration of response was 10.2 months. Median TTP was 11.1 months on sorafenib versus 5.7 months on placebo. A total of 20.3% of the patients in the sorafenib arm and 8.6% of patients in the placebo arm received further anticancer treatment.

Exploratory biomarker analysis to determine predictive/prognostic markers did not reveal any positive results. There was no difference noted in *BRAF* and *RAS* mutated DTCs in this study. Sorafenib showed similar efficacy in all biomarker subtypes studied.

There was no observed difference in outcomes or efficacy in groups with high or low thyroglobulin (Tg) levels. However, it is important to note that patients with high Tg levels demonstrated a fall in levels consistent with partial response (PR). Patients with stable disease demonstrated no change in Tg levels, and upon progression, Tg levels showed a corresponding increase. These results demonstrated the usefulness of Tg monitoring for patients on treatment.

The adverse effects of sorafenib most commonly observed were hand and foot skin reactions, diarrhea, hypertension, and alopecia. These side effects were observed in approximately 70% of patients. Other side effects of fatigue, myalgia, and nausea were also noted. Despite significant toxicities, only 5.6% of patients stopped taking the drug.

STUDY LIMITATIONS

It is important to note that 71.4% of patients in the placebo arm crossed over to sorafenib open-label treatment. This is likely to have led to a confounding effect on the results.

STUDY IMPACT

The landmark DECISION trial is the first randomized controlled trial reporting on systemic treatment for management of DTC. It confirmed efficacy of treatment through demonstration of improved PFS. This trial, being the first and only of its kind, despite its limitations, led to the approval of sorafenib as a systemic treatment option for metastatic and locally recurrent DTC in the first-line setting.

RELEVANT ADDITIONAL STUDIES

The SELECT trial (lenvatinib vs. placebo in RAI-refractory thyroid cancer) is a randomized phase 3, double-blind placebo-controlled trial evaluating management of metastatic thyroid cancer that is iodine refractory.[10] Lenvatinib (Lenvima®, Eisai, Tokyo, Japan) differs from sorafenib in that it is a multitargeted tyrosine kinase inhibitor of the VEGFRs 1, 2, and 3; fibroblast-derived growth factor receptor (FDGFRs) 1–4; platelet-derived growth factor receptor (PDGFR) α; and *RET* and *KIT* signaling networks. The trial objectives were similar to DECISION with PFS as the primary end point and the secondary end points being OS, TTP, and ORR. Cross-over from the placebo arm to the active treatment arm upon progression was also allowed in this trial. Iodine refractory disease in SELECT trial is defined according to at least one of the following criteria: at least one measurable lesion without iodine uptake on any iodine-131 scan, at least one measurable lesion that had progressed according to the Response Evaluation Criteria In Solid Tumors [RECIST] criteria within 12 months after iodine-131 therapy despite iodine-131 avidity at the time of treatment, or cumulative activity of iodine-131 that was >600 mCi and independently reviewed radiologic evidence of progression within the previous 13 months. This differed slightly from the definition of RAI resistance used in the DECISION trial. Subgroup analyses were performed according to age (≤65 years vs. >65 years), sex, geographic region (Europe, North America, or other), histological findings (papillary, poorly differentiated, follicular, or Hürthle cell thyroid cancer),

thyrotropin level (≤0.5, >0.5–2.0, or >2.0–5.5 mIU/L), and receipt or nonreceipt of one prior tyrosine kinase inhibitor treatment.

The results of the SELECT trial were significantly different from DECISION. PFS was 18.3 months versus 10.8 months, as observed in the DECISION trial. Response rates were 68.4% in SELECT trial, which was far superior to the 12.2% noted in the DECISION trial; 1.5% of the patients demonstrated a complete response. Median time to objective response was found to be 2 months. Side effects from treatment were hypertension, proteinuria, arterial thromboembolic effects, venous thromboembolic effects, renal failure including acute renal failure, hepatic failure, gastrointestinal fistula, corrected QT prolongation, and posterior reversible encephalopathy syndrome. A total of 14.3% of patients on lenvatinib stopped their treatment due to toxicity. This was a higher percentage than the 5.6% noted in the DECISION trial.

The SELECT trial was published a year after the DECISION trial. Due to significant improvement in PFS, as well as the better response rates observed in this trial, lenvatinib has become been widely accepted as first-line treatment for metastatic DTC. The DECISION trial, however, remains as the landmark paper, as it was the first clinical trial to confirm efficacy of multikinase inhibitors for management of RAI-refractory progressive DTC.

LIBRETTO 001 (Efficacy of selpercatinib in *RET*-Altered Thyroid Cancers) is an open-label phase 1/2 trial that determined the efficacy of selpercatinib (Retevmo®, Eli Lilly, Indianapolis, Indiana, USA) for targeting *RET* fusion–positive DTC and *RET* mutation–positive medullary thyroid cancer (MTC).[11] This trial also included other *RET* fusion–positive solid malignancies such as lung cancer and others. Germline *RET* mutations result in hereditary syndromes multiple endocrine neoplasia 2a (MEN2a) and MEN2b. *RET* fusion occurs in 60% of sporadic MTCs, while 10% of DTCs will have *RET* fusion detected. Selpercatinib is a highly selective *RET* inhibitor. The primary and secondary objectives of this trial were ORR and PFS, duration of response and safety, respectively. Fifty-five DTC or MTC patients with *RET* fusion and mutation, respectively, were treated with selpercatinib. MTC patients with or without previous treatment were included in the trial, while DTC patients received previous treatments.

This trial confirmed efficacy of the treatment with 69% response rates in previously treated MTC, with a 1-year PFS being 82%. MTC with no previous treatment had a response rate of 73% and PFS of 92%. Previously treated DTC patients demonstrated a response rate of 79% and 1-year PFS of 64%. Overall grade 3 toxicity was low. Only 2% of patients discontinued treatment due to toxicity concerns. Commonly noted toxicities were hypertension (21%), elevated alanine transaminase, elevated aspartate transaminase (9%), hyponatremia (8%), and diarrhea (6%).

The compelling results of this trial, despite being an early phase trial, led to the approval of the use of selpercatinib for treatment of metastatic MTC and DTC after failure of first-line therapy by the Food and Drug Administration (FDA) in the United States as well as by the National Institute of Clinical Excellence (NICE) in the United Kingdom.

Pralsetinib (Gavreto®, Blueprint Medicines Corporation, Cambridge, Massachusetts, USA) is another specific *RET* inhibitor that has also been approved by the FDA for treatment of *RET* mutated and *RET* fusion–positive MTC and DTC, respectively. Efficacy of this drug was tested in the ARROW trial,[12] with results published in 2021. This study had a similar design to LIBRETTO, being an open-label phase 1/2 trial. This trial recruited 122 patients. It has shown response rates similar to selpercatinib. Pralsetinib has slightly higher grade 3 toxicity events compared to selpercatinib. Hypertension, neutropenia, lymphopenia, and anemia are the common grade 3 toxicity events observed. Pneumonitis has also been noted as a grade 3 toxicity in 4% of patients, which is different from selpercatinib. A higher proportion of patients (i.e., 4%) also discontinued treatment due to adverse events.

Larotrectinib (Vitrakvi®, Bayer, Leverkusen, Germany) and entrectinib (Rozlytrek, Genentech, Inc., San Francisco, California, USA), have also become available as treatment options for NTRK fusion–positive thyroid cancers.[13–15] These agents have been used in several basket trials. Thyroid cancer, along with other solid human malignancies, were included in these trials. Overall response rates were noted to be 75% of patients receiving larotrectinib and 57% receiving entrectinib. These responses were noted irrespective of the tumor type. These drugs have now received FDA approval and license for use in the United States.

Cabozantinib (Cabometyx®, Exelixis, Inc., Alameda, California, USA) is a tyrosine kinase inhibitor (TKI) that targets three relevant pathways in MTC: MET, VEGFR2, and RET.[16] This treatment already has FDA approval for the treatment of MTC. The COSMIC-311 trial is a placebo-controlled trial in which DTC patients who had progressed despite treatment with two TKIs were randomized to receive placebo or cabozantinib.[17] A total of 187 patients from centers in 25 countries were randomized in this study between February 2019 and August 2020. The primary efficacy outcome measures were PFS in the intent-to-treat population and ORR in the first 100 randomized patients. Cabozantinib was found to significantly reduce the risk of disease progression or death versus placebo ($p < 0.0001$). The median PFS was 11.0 months (95% CI: 7.4, 13.8) in the cabozantinib arm compared to 1.9 months (95% CI 1.9, 3.7) for those receiving placebo. The ORR was 18% (95% CI: 10%, 29%) and 0% (95% CI 0%, 11%) in the cabozantinib and placebo arms, respectively. This has led to FDA approval of cabozantinib for treatment of progressive DTCs that have failed two previous lines of treatment with TKIs and are ineligible for RAI therapy.

The EXAM trial is a randomized placebo-controlled trial for metastatic and progressive MTC patients.[18] This trial randomized 330 patients for inclusion. The trial met its primary objective, with PFS being 11.2 months compared with 4 months in the placebo arm. However, the secondary end point of OS was not met. This benefit was irrespective of *RET* mutation status. Interestingly, exploratory analysis showed that tumors with a M918T mutation of the *RET* gene had a significantly better OS (44.3 months vs. 18.9 months for placebo). Patients without a *RET* M918T mutation were noted to have a survival of 26.6 months with cabozantinib. Based on these results, cabozantinib was approved by the FDA for treatment of metastatic MTC.

The ZETA trial is also a randomized placebo-controlled trial that evaluated 331 patients. This trial evaluated another TKI, vandetanib (Caprelsa®, AstraZeneca, Cambridge, England, UK)[19,20], which selectively targets RET, VEGFR, and EGFR signaling. The primary end point of this trial was PFS. This trial also met its primary end point, with PFS being 22.6 months versus 16.4 months in the placebo arm. Furthermore, post hoc analysis of the results published in 2020 showed a clinical benefit specifically with prolonged symptom control in addition to PFS improvement. The FDA approved use of this drug for treatment of MTC in 2011. It is important to note that although both vandetanib and cabozantinib have similar efficacy against MTC, with regard to their toxicity profiles, vandetanib has shown better treatment tolerance. This has led to a variation in its utilization among centers treating thyroid cancers.

These *RET* mutation–specific targeting agents (selpercatinib and pralsetinib), as already reviewed, have also been approved for treatment of MTC in the second-line setting, i.e. upon failure of cabozantinib or vandetanib as first-line therapy.

Anaplastic thyroid cancer (ATC) is a rare type of thyroid cancer but one of the most aggressive solid malignancies. Due to its rapid progression, very few treatment options have proven successful. Multimodal treatment with surgery, if and when possible; chemotherapy; anthracycline/taxane and platinum-based combination chemotherapy; and external beam radiation therapy has been used. There has been very little success noted even with aggressive treatment. These cancers invariably prove to be fatal within a short period of time following diagnosis. There have been some encouraging results[21] from a study evaluating *BRAF* V600 mutant cancers treated with dabrafenib (Tafilnar®, Novartis, Dorval, Quebec, Canada)[21] and trametinib (Mekinist®, Novartis, Dorval, Quebec, Canada) in combination. This study included ATC patients previously treated with radiotherapy and/or surgery. Some of these patients had also received systemic treatment. ATC patients who received this treatment demonstrated a 69% response rate, with control rates being 6 months or longer. The FDA approved the use of this combination therapy in 2018.

DTC is generally a highly curable cancer. However, for patients with RAI resistance, the management of relapsed and metastatic thyroid cancer has remained a challenge. Despite poor results and high toxicity, conventional chemotherapy had remained the mainstay of treatment. The DECISION trial first brought to the frontline an effective biological targeted therapeutic option, i.e., sorafenib, a multikinase inhibitor. Since the publication of this trial in 2014, the therapeutic landscape for RAI-refractory disease has changed considerably. Now there are several therapeutic options available, and further studies are being pursued for additional development (Table 26.1). Lenvatinib (SELECT) has gained favor over sorafenib due to improved response rates. Cabozantinib (COSMIC 311) is also now available as a second-line treatment option. Selpercatinib and pralsetinib (LIBRETTO 001 and ARROW, respectively) have also been approved for therapy of *RET* fusion–positive DTC upon failure of first-line treatment. MTC, the second most common subtype of thyroid cancer, also has new treatment options. The TKIs cabozantinib (EXAM) and vandetanib (ZETA) have been approved for use to treat metastatic MTC. MTC that is sporadic or familial (MEN2a and MEN2b) carry a *RET* mutation. Therefore, these cancers are amenable to treatment with selpercatinib and

Table 26.1 Summary of reviewed clinical trials

Clinical Trial	Trial Design	Drug Evaluated	Outcomes
DECISION	Phase 3 randomized	Sorafenib vs. Placebo	Median PFS 10.8 vs. 5.8 months
SELECT	Phase 3 randomized	Lenvatinib vs. Placebo	Median PFS 18.3 vs. 10.8 months
LIBRETTO 001	Phase1/2 trial	Selpercatinib vs. Placebo	1-yr PFS 92% and RR of 73% in treatment-naïve patients 1-yr PFS 82% and RR 69% in previously treated patients
ARROW	Phase1/2 trial	Pralsetinib vs. Placebo	PFS not reached
COSMIC-311	Phase 3 randomized	Cabozantinib vs. Placebo	Median PFS 11.0 vs. 1.9 months
EXAM	Phase 3 randomized (MTC only)	Cabozantinib vs. Placebo	PFS 11.2 vs. 4 months for patients with *RET* M918T mutation OS 44.3 vs. 26.6 if no *RET* M918T mutation
ZETA	Phase 3 randomized (MTC only)	Vandetanib vs. Placebo	PFS 22.6 vs. 16.4 months

Abbreviations: MTC, medullary thyroid cancer; OS, overall survival; PFS, progression-free survival; RR, Response rate.

pralsetinib as second-line treatment options (FDA approved). ATC remains a challenge. Radiotherapy and/or surgery and chemotherapy remain up-front treatment options. However, in patients with a *BRAF* V600 mutation, dabrafenib and trametinib have been approved for treatment. There are several trials with combinations of different novel targetable agents, including immunotherapy, currently being conducted. In an open-label phase 1/2 study with the immune checkpoint inhibitor spartalizumab (Novartis, Dorval, Quebec, Canada)[20] encouraging responses have been observed. This will require further evaluation and confirmation in subsequent clinical trials.

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Chapter 27

Anaplastic Carcinoma

Review by Lucy Li and Omar Hilmi

Landmark Paper

DABRAFENIB AND TRAMETINIB TREATMENT IN PATIENTS WITH LOCALLY ADVANCED OR METASTATIC BRAF V600-MUTANT ANAPLASTIC THYROID CANCER

Subbiah V, Kreitman RJ, Wainberg ZA, Cho JY, Schellens JHM, Soria JC, Wen PY, Zielinski C, Cabanillas ME, Urbanowitz G, Mookerjee B, et al. *J Clin Oncol.* 2018;36(1): 7–13. doi:10.1200/JCO.2017.73.6785

RESEARCH QUESTION/OBJECTIVES

Anaplastic thyroid cancer (ATC) is the rarest thyroid cancer subtype, accounting for less than 1% of all thyroid cancers.[2] ATCs are associated with an aggressive clinical course and very poor prognosis, with a historical median overall survival (OS) of ~5 months following initial diagnosis and 1-year overall survival of 10–20%.[3,4] Although they can arise de novo, they are usually derived from, and can coexist with, differentiated thyroid cancer (DTC), therefore retaining the mutations of the tumor from which they originate.[5] Standard treatment of ATC involves a multimodal approach with surgery, chemotherapy, and external beam radiotherapy, now associated with an improved median OS of approximately 9 months.[6] However, aggressive approaches to treatment can be associated with significant side effects and toxicities. Furthermore, due to disease extent at the time of initial diagnosis, many ATC patients may be inoperable or suitable for palliative surgery only. There has been limited evidence to conclusively demonstrate improved survival or quality of life in response to systemic therapy in patients with advanced disease, underscoring the critical need for the development of novel treatment approaches.[7]

The advancement of molecular profiling has elucidated the role of somatic mutations in the development of ATCs and may also direct individualized targeted therapy.[8,9] Between 20% and 50% of ATCs have been found to have a mutation in their *BRAF* gene, a key component of the mitogen-activated protein kinase (MAPK) pathway involved in the regulation of cellular growth, proliferation, and differentiation.[8–10] When ATC coexists with papillary thyroid cancer (PTC) in the pathology specimen, >90% may harbor a *BRAF* V600 mutation. Signal transduction continues downstream from *BRAF* to MAPK kinase (MEK)1 and MEK2, resulting in the phosphorylation of multiple targets.[10]

Although several clinical trials with BRAF inhibitor monotherapy demonstrated a high rate of objective response and improved OS, approximately half of the patients developed

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disease progression within 6–7 months of treatment initiation.[11,12] Resistance is thought to be mediated through reactivation of the MAPK pathway through mechanisms including upstream activating mutations (e.g., *NRAS* or *KRAS* mutations), activation of parallel signaling pathways (e.g., PI3K), and increased tyrosine kinase receptor expression (e.g., endothelial growth factor receptor [EGFR], platelet-derived growth factor receptor [PDGFR]).[10] Furthermore, *BRAF* inhibitor monotherapy was shown to be associated with hyperproliferative cutaneous events, such as keratoacanthoma and squamous cell carcinoma.[10] Combining treatment with a MEK1/2 inhibitor such as trametinib was therefore postulated to maximize MAPK pathway inhibition and prevent resistance. Studies have since demonstrated treatment targeting both *BRAF* and MEK kinases enhances antitumor activity compared with targeting *BRAF* inhibitor alone by delaying or preventing resistance, as demonstrated in transgenic mouse models, of *BRAF* V600–mutant ATC.[13] Similar findings were also reported in clinical trials of patients with *BRAF* V600–mutant metastatic melanoma and non–small cell lung cancer, where treatment with combined *BRAF* and MEK inhibition increased overall response frequency, duration of response, progression-free survival (PFS), and OS compared with *BRAF* monotherapy.[14–16]

The aim of this landmark paper was to investigate the clinical efficacy and safety of dabrafenib (*BRAF* inhibitor) and trametinib (MEK inhibitor) combination therapy in patients with locally advanced or metastatic *BRAF* V600–mutated ATC.[1]

STUDY DESIGN

This was a multicenter, open-label, nonrandomized clinical trial of ATC patients with a known *BRAF* V600E mutation. The primary outcome was investigator-assessed overall response rate (ORR) based on Response Evaluation Criteria In Solid Tumors (RECIST) v1.1.[17] Secondary end points included duration of response, PFS, OS, and safety. The study was designed, conducted, and analyzed by the funder (Novartis Pharmaceuticals, Basel, Switzerland) in conjunction with a steering committee.

SAMPLE SIZE

The study reported on 16 patients with *BRAF* V600E–mutated ATC. The safety population comprised 100 patients with *BRAF* V600E–mutated rare cancers.

INCLUSION/EXCLUSION CRITERIA

Inclusion Criteria	Exclusion Criteria
Age ≥ 18 years	Prior *BRAF* and/or MEK inhibitor(s) treatment
No standard locally or regionally available treatment options	Prior radiotherapy within 7 days of enrollment
Measurable disease based on RECIST v1.1 (17)	Unresolved treatment-related adverse events
Tissue available for *BRAF* V600E mutation analysis	Tumors potentially curable by surgical excision alone
Eastern Cooperative Oncology Group performance status: 0, 1, 2 (18)	Standard-of-care treatment not received
Able to swallow oral medication	Previous thyroid lymphoma, sarcoma, or metastatic disease from other sites
Adequate baseline organ function	

INTERVENTION OR TREATMENT RECEIVED

Patients received oral dabrafenib (Novartis, Switzerland) 150 mg twice daily in combination with oral trametinib (Novartis, Switzerland) 2 mg once daily until disease progression, unacceptable toxicity, or death.

RESULTS

All patients received prior radiation treatment and/or surgery, and six had received prior systemic therapy. ORR was 69% (11 of 16; 95% confidence interval [CI]: 41–89) in patients treated with dabrafenib and trametinib, with one complete response and ten partial responses. Kaplan-Meier estimates at 12 months duration of response, PFS, and OS were 90%, 79%, and 80%, respectively. Across all histological cohorts, 93% of patients experienced any adverse event (AE), most commonly fatigue (38%), pyrexia (37%), and nausea (35%). Forty-two percent of patients experienced grade 3 or 4 events, the most common being fatigue, anemia, and neutropenia (all 5%). Thirty percent of patients had an AE that led to a dose reduction, 38% resulting in a dose interruption/delay, and 8% resulting in permanent discontinuation.

STUDY LIMITATIONS

The study cohort size was small, being composed of only 16 patients, although this is likely to reflect the rarity of the disease. The study had a nonrandomized design, which could have introduced bias that affected the results. Patients who were unable to swallow pills were excluded; therefore, the patients enrolled may have had a lesser burden of locoregional disease in their necks, potentially biasing results. Independent central confirmation of pathology diagnosis was also not performed.

Although these results require further confirmation with future clinical studies, conducting a randomized clinical trial in this setting is challenging given the low incidence of ATC combined with its aggressive clinical course, poor prognosis, and lack of clinical equipoise.

STUDY IMPACT

This phase 2, open-label trial demonstrated that dabrafenib in combination with trametinib has revolutionized treatment for patients diagnosed with locally advanced or metastatic *BRAF* V600E–mutated ATC. The overall response rate was 69% after a median follow-up of 47 weeks, with most responses occurring early in the treatment course. Kaplan-Meir estimation of 12-month OS was 80%, significantly higher than the historical survival rate. This study represents the best response of any targeted therapy trial to date by ATC. It should, however, be highlighted that combination therapy was associated with a high rate of AEs, with 93% of patients in the safety cohort experiencing any AE, highlighting the importance of effectively managing toxicities early during treatment.[18] Based on the interim results published for this study, the Food and Drug Administration (FDA) approved combination therapy with dabrafenib and

trametinib for treatment of patients diagnosed with *BRAF* V600E–mutated ATC with locally advanced, unresectable, or metastatic disease in May 2018, with multiple international guidelines now incorporating molecular profiling for the *BRAF* V600E mutation at the time of diagnosis.[4,7] This landmark article included 15 participants and 1 from an expansion cohort; however, the study continued to recruit patients until July 2018, which increased their expansion cohort by 21, and so outcomes for a total of 36 ATC patients were reported in January 2022. Though the reported patient outcomes in this update were not as encouraging as previously described (ORR 56%, 12-month PFS 43.2%, and OS 51.7%), it still confirmed the substantial clinical benefit and manageable toxicity identified in the original study.[19]

There is evidence to suggest combination treatment with *BRAF*/MEK inhibitors and immune checkpoint inhibitors may enhance the durability of the antitumor response. *BRAF* inhibition is thought to result in increased tumor infiltration by CD4+ and CD8+ T cells that drive tumor lysis, as well as an increase in PD-L1 expression.[20,21] The phase 2, Keynote-022 study showed pembrolizumab (Merck, Germany, a PD-1 receptor inhibitor, combined with dabrafenib and trametinib improved PFS without reaching statistical significance in *BRAF*-mutant melanoma (median PFS 16.9 vs. 10.7 months; hazard ratio [HR] 0.53, CI 0.34–0.83).[22] However, patients treated with this triple therapy had a higher incidence of ≥ grade 3 AEs (58% vs. 25%), including one death from pneumonitis related to treatment. Further research is required to characterize the risk-benefit profile of combination treatment with immune checkpoint inhibitors and targeted inhibitor therapy – for example, through intermittent dosing regimens or different immunotherapy/targeted inhibitor therapy combinations in order to maintain the benefits of triple therapy while reducing toxicity.

RELEVANT ADDITIONAL STUDIES

There have been several additional targeted therapy trials for ATC; however, they have largely consisted of single-arm studies with small patient numbers and modest results. Studies that use mutational analysis to stratify patients, such as the selected landmark article, offer more promising outcomes. For example, in a "basket" study of vemurafenib (Roche, Switzerland) for treatment of *BRAF* V600–positive nonmelanoma cancers, there was one complete response (14%), representing the only other complete response to treatment to date from ATC, and one partial response (14%) in a cohort of seven ATC patients.[23] Several case reports have also shown treatment responses to vemurafenib in patients with *BRAF* V600E–mutated ATC.[24,25] Similarly, everolimus (Novartis, Switzerland), a mammalian target of rapamycin (mTOR) inhibitor, demonstrated longer PFS in patients with mutations in the P13K/mTOR/AKT pathway that is involved in cell proliferation and apoptosis.[26] Other studies have focused on the use of multikinase inhibitors (MKIs), such as sorafenib (Bayer, Germany), lenvatinib (Eisai and Merck & Co USA), pazopanib (GlaxoSmithKline/Novartis, UK/Switzerland), and sunitinib (Pfizer, USA) that can act on more than one target simultaneously and are thought to have a synergistic effect when used in combination.[27] For example, although sorafenib, a *RAF*, VEGFR, and PDGFR inhibitor, demonstrated an improvement in PFS of 5 months in phase 3 clinical trials compared to the placebo group, resistance invariably developed

after 1–2 years of treatment.[28] Additional salvage therapy with sunitinib, pazopanib, cabozantinib, lenvatinib, and vemurafenib resulted in a partial response in 41% (7/17) of patients and stable disease in 59% (10/17) of patients. Median PFS was 7.4 months with first-line sorafenib and 11.4 months with salvage therapy.[29]

Clinical trials focused on ATC are limited by the rarity of the disease and its rapid disease progression. Therefore, international multicenter studies in the future are required to overcome this challenge. Further characterization of the tumor-specific mutational landscape through molecular profiling can help identify potential therapeutic targets to develop individualized treatment plans for ATC patients. Additional trials investigating the role of targeted therapy as part of multimodal disease management, as well as in combination with immunotherapy, are needed in the future.

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Chapter 28

Medullary Carcinoma

Review by Aleix Rovira, Paul V. Carroll, and Ricard Simo

Landmark Paper

PROPHYLACTIC LATERAL NECK DISSECTION FOR MEDULLARY THYROID CARCINOMA IS NOT ASSOCIATED WITH IMPROVED SURVIVAL

Spanheimer PM, Ganly I, Chou JF, Capanu M, Nigam A, Ghossein RA, Tuttle RM, Wong RJ, Shaha AR, Brennan MF, Untch BR. *Ann Surg Oncol.* 2021;28(11):6572–6579. doi: 10.1245/s10434-021-09683-8

RESEARCH QUESTION/OBJECTIVES

Lymphatic spread with nodal metastases occurs very commonly in medullary thyroid carcinoma (MTC) and is a significant risk factor for disease recurrence and death in this thyroid cancer patient population. Lymph node dissection (LND) as part of the initial surgical treatment strategy is crucial in the management of MTC with macroscopic radiologically evident disease. However, the extent of LND at the time of total thyroidectomy in the absence of structural disease, as assessed radiologically, has remained controversial, particularly with regard to the extent of lateral neck LND (LLND). Calcitonin (Ct) and carcinoembryonic antigen (CEA) are important tumor markers of MTC. Current guidelines recommend that the extent of the LND can be decided according to the serum Ct levels. However, Ct does not correlate well with long-term oncological outcomes and neck recurrences even after LND.[1]

The primary aim of this single institution-based landmark paper was to characterize long-term oncological outcomes for MTC patients and to describe variables associated with those outcomes. Importantly the authors examined the impact of prophylactic LLND (pLLND) in patients with basal serum Ct levels greater than 200 pg/mL but with no evidence of structural lateral neck disease.

STUDY DESIGN

Retrospective cohort study carried out at Memorial Sloan Kettering Cancer Center, New York. Data was included from the years 1986 to 2018.

SAMPLE SIZE

Three hundred and sixteen patients underwent thyroidectomy for treatment of MTC with a curative intent.

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INCLUSION/EXCLUSION CRITERIA

Three hundred and forty MTC patients were identified for possible study inclusion. Of these there were 20 with metastatic disease and 4 with gross residual disease following thyroidectomy who were excluded, leaving a total of 316 patients who underwent thyroidectomy with a curative intent.

INTERVENTION/TREATMENT RECEIVED

At the time of total thyroidectomy, LND was performed at the discretion of the operating surgeon, as summarized in Table 28.1. All patients with evidence of structural lymph node disease underwent formal dissection of the involved neck compartment(s). Levels II–V were classified as the LLND and designated as ipsilateral or contralateral to the primary site of the thyroid cancer. The central neck was defined as levels VI and VII. To examine the impact of pLLND, the subset of the study patient population that had no evidence of structural disease in their lateral neck(s) and that had a preoperative basal serum Ct greater than 200 pg/mL was further analyzed. Eighty-nine patients met these criteria, of whom 45 underwent an ipsilateral lateral pLLND and 44 did not (no LLND). A Ct measurement of 200 pg/mL was used as a cutoff, as this has been used as a recommendation for bilateral pLLND.[2]

RESULTS

The 5-year locoregional recurrence (LRR) cumulative incidence was 28% (95% confidence interval [CI] 23–34%) and the 10-year cumulative incidence was 39% (95% CI 32–45%). Of the 61 patients who experienced a lymph node recurrence in the ipsilateral lateral neck, 33 (54%) previously underwent ipsilateral LLND as part of their initial operation.

Factors associated with LRR on univariate analysis included tumor size (hazard ratio [HR] 1.15 [95% CI 1.06–1.24], $p = 0.001$), preoperative Ct level (HR 1.27 [95% CI 1.09–1.48], $p = 0.003$), postoperative Ct level (HR 1.23 [95% CI 1.14–1.32], $p < 0.001$), postoperative CEA level (HR 1.23 [95% CI 1.07–1.41], $p = 0.003$), positive lymph nodes (HR 3.43 [95% CI 2.18–5.39], $p < 0.001$), and persistent biochemical disease defined as elevation in the first postoperative Ct or CEA (HR 7.8 [95% CI 3.61–16.7], $p < 0.001$). After controlling for tumor size, postoperative CEA level, and structural disease, factors independently associated with LRR by multivariable analysis were postoperative Ct level (HR 1.23 [95% CI 1.08–1.39], $p < 0.001$) and lymph node positivity (HR 2.35 [95% CI 1.21–4.57], $p = 0.01$).

Table 28.1 Neck management summary

Type of Neck Dissection	Number of Patients	Percent (%)
Central + Ipsilateral LLND	95	30
Central Neck Dissection	87	28
Ipsilateral LLND Only	36	11
Central + Bilateral LLND	23	7
Bilateral LLND	2	1

Abbreviation: LLND: *Lateral lymph node dissection.*

Table 28.2 Recurrence, survival, and reoperation rates

Outcome	Ipsilateral LLND	No Ipsilateral LLND	*p*-Value
10-yr LRR	21% (95% CI 9%–37%)	30% (95% CI 9%–37%)	$p = 0.46$
10-yr DR	18% (95% CI 6%–36%)	18% (95% CI 5%–38%)	$p = 0.97$
10-yr DSS	86% (95% CI 71%–100%)	93% (95% CI 80%–100%)	$p = 0.53$
10-yr OS	82% (95% CI 80%–100%)	90% (95% CI 76%–100%)	$p = 0.60$
Reoperation	16% (95% CI 5%–31%)	23% (95% CI 8%–42%)	$p = 0.43$

Abbreviation: CI: *Confidence interval*; *DR*: *Distant recurrence*; *DSS*: *Disease-specific survival*; *LLND*: *Lateral lymph node dissection*; *LRR*: *Locoregional recurrence*; *OS*: *Overall survival*.

Among the subset of patients ($n = 89$) who had no evidence of structural disease and a preoperative Ct > 200 pg/mL, 45 underwent ipsilateral pLLND and 44 did not. There was no difference between these two cohorts in tumor size, postoperative Ct (median 16 vs. 16 pg/mL, $p = 0.9$) or CEA (median 6 vs. 5 ng/mL, $p = 0.5$) levels, persistent biochemical disease at time of the first postoperative laboratory evaluation (59% vs. 49%, $p = 0.50$), or surgical era when surgery was undertaken. The group that underwent ipsilateral pLLND were, however, younger than those that did not (median 50 vs. 58 years). Survival and recurrence outcomes as well as reoperation rates were not significantly different between these two patient groups (Table 28.2). Among patients who underwent a pLLND, five had LRR: two (40%) in the central neck, two (40%) in the ipsilateral lateral neck only, and one (20%) in the ipsilateral lateral and contralateral lateral necks. In the no LLND group, there were six who experienced an LRR: two (33%) in the central neck and four (67%) in the ipsilateral lateral neck.

STUDY LIMITATIONS

The main limitation of this study was its retrospective nature, which relied on cancer registry records from a single institution. This limitation, along with the lack of randomization between the two interventions investigated (pLLND vs. no pLLND), may have led to a selection bias. No comment is made as to whether patients with hereditary disease were included. The study also included patients treated over several decades, and although no differences were reported between different evaluated periods, new treatments (such as adjuvant therapies) and more accurate imaging and diagnostic techniques have been developed over recent years, potentially changing the profile of patients with preoperative "structural disease." On that note, only 64% of the study patients actually underwent preoperative imaging.

In the study population, the no-pLLND patients were older than the pLLND patients, which would bias that group toward worse survival outcomes. Lastly, associations of LND status with overall survival (OS), disease-specific survival (DSS), time to LRR, and time to distant recurrence (DR) were based on a subset of 89 patients and thus should be interpreted with caution, as a type II error may have occurred (i.e. too few

patients analyzed to demonstrate a difference between groups). From this point of view, it is worth noting that the LRR was nonsignificantly higher in the no-pLLND group than in those who underwent pLLND.

STUDY IMPACT

This is the first study that analyzed recurrence and survival related to the extent of LND for MTC. Having acknowledged its limitations, this study showed that ipsilateral pLLND in MTC patients who have no evidence of structural disease in in their lateral neck compartment is not associated with improved survival, even in patients with a preoperative Ct of >200 pg/mL. The findings of similar recurrence and survival rates in patients treated with or without ipsilateral pLLND indicates that the potential for residual microscopic lymph node disease does not increase the risk of subsequent metastases and that LRR is salvageable with neck dissection.

Similarly, randomized controlled trials in breast cancer (ACOSOG Z0011)[3] and cutaneous melanoma (MSLT-2)[4] have demonstrated the safety of nodal observation strategies and have shown no survival advantage with complete prophylactic lymphadenectomy in select patients with nodal disease. These findings are consistent with a model of disease progression where systemic disease does not result from the stepwise progression through the lymph nodes.

The findings from this landmark paper will influence thyroid cancer treatment teams and clinicians in surgical decision-making for the management of MTC. Using national/international guidance, bilateral pLLND is currently commonly performed, even in the absence of radiologically evident disease. This paper supports both strategies of ipsilateral pLLND and no ipsilateral pLLND in this population of patients. The current era of specialist teams with high-resolution ultrasound and other imaging modalities has increased preoperative accuracy and assessment of MTC patients. This study highlights the need for prospective randomized studies in order to facilitate a less aggressive approach in MTC patients without radiologically diagnosed lateral compartment LND.

RELEVANT ADDITIONAL STUDIES

Sporadic MTC is a Ct-secreting neuroendocrine malignancy with a slow growth rate and is believed to take 10 years or longer to become symptomatic.[5] This creates an opportunity for early diagnosis of preclinical disease by prophylactic interventions such as LND. Preoperative Ct and CEA measurements are correlated with tumor burden and so can be used in combination with imaging to assess the extent of disease at diagnosis. Multiple studies highlighting the relevance of biochemical Ct screening were published in the late 1990s,[6–10] and consequently it is measured routinely in the assessment of patients with thyroid nodules in Europe.[11] However, in other parts of the world, this has not been strongly recommended due to concerns regarding its cost-effectiveness.[12]

Current guidelines state that the extent of the LND can be determined according to the preoperative Ct levels[12–14] (Table 28.3). This is based on several previously published

Table 28.3 Guidelines regarding neck management for MTC treatment

Neck Dissection Type	ATA[12]	BTA[13]	ETA[14]
CND	Always (level VI)	Always (levels VI and VII)	Always except small MTC + Ct < 20 pg/mL
Ipsilateral ND	Depending on Ct	Depending on Ct or CND frozen section	Ct levels 50–200 pg/mL
Contralateral ND	If ipsilateral involvement and Ct > 200 pg/mL	If CND or ipsilateral involvement	Ct level > 200 pg/mL

Abbreviation: ATA: *American Thyroid Association*; *BTA*: *British Thyroid Association*; *CND*: *Central compartment neck dissection*; *Ct*: *Calcitonin; ND*: *Neck dissection*.

studies identifying Ct as an important biomarker for MTC tumor size and lymph node metastasis, including an important study published by Machens and Dralle in 2010.[2] According to the results of this study, which analyzed the clinical utility of pretherapeutic serum Ct levels for predicting the extent of lymph node metastasis and dissection in 300 MTC patients, ipsilateral LND and cCND should be the minimum extent of neck dissection performed for treatment of MTC, and bilateral LND should be undertaken when Ct levels >200 pg/mL to reduce the risk of LRR. This more aggressive approach is at odds with the current reviewed landmark paper, which argues for more conservative surgical management. Apart from preoperative Ct levels, other parameters that have been shown to predict the presence of occult lymph node metastasis include preoperative CEA levels,[2,15] the presence of extrathyroidal cancer extension, and larger cancer size.[15,16]

The occult metastasis rate in MTC has been reported to be between 23% and 14% in the ipsilateral and contralateral necks, respectively.[17] A meta-analysis reported by Kim et al. that included 15 studies found an overall rate of lymph node metastasis of 22.9%, even in patients diagnosed with micromedullary thyroid carcinoma (tumor <1 cm in maximum diameter).[18] For head and neck squamous cell carcinoma, a 20% or greater risk of occult neck disease is the accepted threshold for indicating a pLND.[19] However, as MTC is an uncommon disease, most articles have reported retrospective single-institution data on diverse patient groups with heterogeneous surgical approaches, and consequently the evidence base for recommendations for pLLND in the management of occult neck disease is weak. Clinical guidelines defer the necessity of pLLND for MTC due to the increased operative time, cost, and associated patient morbidity, but more importantly due to a lack of evidence showing a survival advantage associated with pLLND.

Two articles analyzing Surveillance, Epidemiology, and End Results (SEER) data reported that pLLND does not improve the OS of MTC patients. The first article concluded that although the number of positive nodes is relevant, the number of nodes examined had no impact on survival.[20] Another study showed that pLLND has a survival advantage, but only for patients with distant metastasis.[21]

American Thyroid Association (ATA) guidelines[12] recommend ipsilateral pLLND when Ct is higher than or equal to 20 pg/mL and bilateral pLLND when Ct is higher than or equal to 200 pg/mL. However, reporting on a cohort of 66 patients, investigators from MD Anderson in 2018 were unable to identify any benefit in the rates of biochemical cure, LRR, DR, or OS with pLLND performed in patients with no preoperative evidence

of lateral neck disease by imaging.[22] This cohort included 93% of patients with Ct levels over 20 pg/mL and 68% of patients with Ct over 200 pg/mL in the observation group. Although there was no significant difference in age, stage, preoperative serum CEA level, and preoperative serum Ct level between the groups, the preoperative median Ct level was noted to be significantly higher in those who underwent pLLND, possibly acting as a confounder.[22]

Juez et al. in a recent multicenter retrospective review of 244 MTC patients once again reported that baseline Ct level was a good predictor of nodal involvement (area under the curve [AUC] 0.718 and 95% CI 0.66–0.978).[23] New higher thresholds for pLLND were proposed for sporadic tumors based on a <10% probability of lymph node involvement: bilateral pLLND was recommended when basal Ct > 600 pg/mL and ipsilateral pLLND when basal Ct was 240–599 pg/mL. In contrast, Ahn et al. published a meta-analysis that aimed to determine the clinical benefits of pLLND in clinically overt MTC, including sporadic or index cases of the familial type.[24] The results of their analysis of 18 studies that included 1,696 patients showed that the frequency of ipsilateral LLND significantly improved DSS ($p = 0.017$).

In conclusion, consensus guidelines regarding the management of the neck in MTC patients have relied on expert opinion due to a relative absence of high-quality data. The recommendations for ipsilateral and bilateral pLLND in MTC patients without structural evidence of cervical lymph node metastases but with Ct >200 pg/mL fall into this category. Whether prophylactic removal of subclinically involved lymph nodes influences disease behavior and improves survival is not certain. Multidisciplinary teams and tumor boards currently make treatment decisions for MTC patients on a case-by-case basis, using best evidence and their experience. Based on the landmark paper reviewed and other emerging evidence, we agree that in some MTC patients the absence of macroscopic disease after careful radiological evaluation means that pLLND in the lateral compartments (II–V) is not mandatory, and this holds true regardless of the serum Ct level.

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CHAPTER 29

MEN2: Medullary Carcinoma

Review by Yi Sia and Radu Mihai

Landmark Paper

PROPHYLACTIC THYROIDECTOMY IN MULTIPLE ENDOCRINE NEOPLASIA TYPE 2A

Skinner MA, Moley JA, Dilley WG, Owzar K, Debenedetti MK, Wells SA Jr. *N Engl J Med.* 2005;353(11):1105–1113. doi: 10.1056/NEJMoa043999

RESEARCH QUESTION/OBJECTIVES

Patients diagnosed with multiple endocrine neoplasia (MEN) type 2A and type 2B will almost inevitably develop medullary thyroid carcinoma (MTC) during their lifetime, with MTC being the most common cause of death in this population.[1–4] Total thyroidectomy performed before MTC develops, or when it is still confined to the thyroid gland, remains the only curative treatment to date.

With the discovery of mutations in the *RET* proto-oncogene as the cause of MEN2 syndromes in the early 1990s, it became possible to identify by direct DNA analysis persons within such kindreds who have inherited the mutated *RET* allele and in whom MTC is destined to develop.[5–7] This discovery revolutionized treatment for these at-risk patients, providing a rationale for total thyroidectomy early in life either before MTC develops or when it is confined to the thyroid gland.

This study was the first to assess the effectiveness of thyroid surgery in young patients with the MEN2A genotype by examining their clinical and biochemical status at 5 (or more) years after total thyroidectomy. The study also explored if the outcome of surgery was related to the specific *RET* codon mutation, the preoperative stimulated plasma calcitonin level, the age of the patient at the time of surgery, the histological status of the thyroidectomy specimen, the presence or absence of cervical lymph node metastases, or a combination of all these factors.

STUDY DESIGN

Longitudinal study of consecutive patients operated at in two centers (Duke and Washington University) after being identified as having MEN2A via a genetic screening program initiated in 1993 at the Department of Surgery, Washington University School of Medicine, St. Louis, USA.

SAMPLE SIZE

Fifty patients with MEN2A who underwent total thyroidectomy by one of four surgeons.

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INCLUSION/EXCLUSION CRITERIA

Patients who were aged 19 years or younger at the time of total thyroidectomy and in whom evidence of MTC was evaluated for at least 5 years postoperatively were included in the study. Patients who were older than 19 years at the time of surgery and those followed up for less than 5 years postoperatively were excluded.

INTERVENTION OR TREATMENT RECEIVED

Medical history and physical examination were obtained from each patient. Plasma calcitonin levels were determined before and after provocative testing with calcium and pentagastrin.[8] One of four surgeons performed a total thyroidectomy following an established protocol of removing the entire thyroid gland and the central compartment lymph nodes. Parathyroid glands were removed and autotransplanted into muscle, either into the nondominant forearm (if a patient had a *RET* mutation associated with a high incidence of parathyroid hyperplasia) or into the neck.[9]

Patients were commenced on calcium and vitamin D postoperatively and were discharged once serum calcium levels were normal or near normal and after a calcium-pentagastrin stimulation test was performed. Thereafter, follow-up was in collaboration with the patients' referring physicians and included annual physical examination and intermittent calcitonin testing.

At 5 or more years after total thyroidectomy, all patients were evaluated by physical examination and had their plasma calcitonin levels measured.

RESULTS

Forty-four of the 50 patients (88%) had no evidence of persistent or recurrent disease after total thyroidectomy, as demonstrated by plasma calcitonin levels at or below the detection limit before and after calcium-pentagastrin stimulation.

The six patients who had evidence of persistent or recurrent MTC were all older than 8 years of age at the time of surgical intervention. There was no statistical evidence to suggest that persistent or recurrent disease was dependent on specific codon mutations ($p = 0.92$). Regional lymph node metastasis did, however, appear to play a role in predicting persistent or recurrent disease, as patients with negative nodes were found to have a lower incidence of persistent or recurrent MTC than those with positive nodes ($p = 0.04$). This led the authors to conclude that there was a lower incidence of persistent or recurrent disease in children who underwent total thyroidectomy before 8 years of age and in whom there was no evidence of cervical lymph node metastases.

There were 17 patients (median age, 6 years) who had either no evidence of disease or isolated C-cell hyperplasia on histopathology, compared to 33 patients (median age, 10 years) who had microscopic or macroscopic MTC. The difference in age distribution between these two groups was significant ($p = 0.02$).

The age distribution of the 27 patients (median age, 11 years) with elevated preoperative plasma calcitonin levels after stimulation also appeared to differ, albeit slightly, from that of the 23 patients (median age, 7 years) with normal preoperative levels ($p = 0.05$).

Postoperative serum calcium levels were evaluated at least 1 year after surgery in all patients. Serum calcium levels were normal in 47 of the 50 patients (94%). In three patients, calcium and vitamin D supplements were required to maintain the serum calcium levels within or near the normal range.

STUDY LIMITATIONS

The relatively small study patient population could be considered a limitation. This must be viewed in the context of the sparsity of MEN2 families across the world. Outside of a few institutions with an established research program for MEN2 or MTC, most thyroid surgeons may never encounter a MEN2 family during their professional life. Having operative and follow-up data on 50 patients with MEN2 is an achievement difficult to match even two decades after the publication of this landmark paper.

The extent of the operations performed on the study patients was more aggressive than what is currently practiced. The inclusion of central compartment lymph node dissection in all patients was deemed beneficial at that time, but such an aggressive approach is currently considered only when the operation is performed later than the age recommended by guidelines and if serum calcitonin levels are elevated.[10] Removing all parathyroid glands and transplanting them into an area with easier access (forearm muscle) is also currently unlikely to be routinely performed in current practice.

STUDY IMPACT

This study demonstrated that when total thyroidectomy is performed in children before the age of 8 years, there is a lower incidence of persistent or recurrent MTC across a follow-up period of at least 5 years. The data revealed that it may be unnecessary to perform central neck compartment lymph node dissection in patients of this age, since none of the patients younger than 11 years of age had lymph node metastases at the time of their total thyroidectomy. The authors also reported a low incidence of persistent postoperative hypocalcemia (6%), suggesting that in "expert hands," thyroid surgery in young patients with *RET* gene mutations is safe.

RELEVANT ADDITIONAL STUDIES

Early detection and intervention for hereditary MTC has been shown to significantly alter the course of the disease and its associated mortality.[11] A year after the discovery of mutations in the *RET* proto-oncogene as being the cause of MEN2A in 1993, Wells et al. published their first results in patients who underwent total thyroidectomy and central neck dissection on the basis of genetic testing.[12] Of the 13 out of 21 patients with inherited *RET* mutation who chose immediate thyroidectomy, only 4 had macroscopic evidence of MTC, while the rest had microscopic disease and/or C-cell hyperplasia. All 13 patients had C-cell hyperplasia with or without MTC confined to the thyroid gland,

and all had normal stimulated postoperative serum calcitonin levels. This study led the authors to propose that patients should be offered thyroidectomy as soon as a *RET* mutation associated with MEN2A is identified, regardless of age. Although the authors recommended thyroidectomy for children as young as 5 years of age, the optimal timing for prophylactic thyroidectomy and the extent of surgery remained to be determined.

Over the following years, Dralle et al. published results on 75 children and adolescents who underwent prophylactic thyroidectomy in Germany and Austria and showed that increasing age was associated with a higher probability of C-cell pathology, as well as an increased risk of lymph node metastases.[13] All patients older than 10 years of age had at least bilateral C-cell hyperplasia, although there were patients as young as 4 years old who had progressed to MTC. The authors recommended thyroidectomy at approximately 6 years of age. Meanwhile, lymph node metastases rarely occurred before 10 years of age and, when present, were accompanied by elevated calcitonin levels, either at baseline or after stimulation. Therefore, it was inferred that prophylactic thyroidectomy without lymph node dissection was adequate for children younger than 10 years of age in the absence of elevated post-stimulated calcitonin levels. Central compartment lymph node dissection was recommended in those children with elevated stimulated calcitonin and those older than 10 years.

Currently it is known that certain *RET* mutations are associated with more aggressive MTC. The Seventh International Workshop on MEN created a three-tier classification system for *RET* mutations based on aggressiveness of MTC,[14] which was further expanded by the American Thyroid Association (ATA) Medullary Thyroid Cancer Guidelines in 2009 into a categorization system consisting of four levels (ATA-A to ATA-D), from "least high" risk (MEN2A or familial MTC) to highest risk (MEN2B) of developing aggressive MTC. This was subsequently updated in the more recent 2015 ATA guidelines into ATA-HST (highest risk, for those with MEN2B), ATA-H (high risk, MEN2A with *RET* codon 634 mutation), and ATA-MOD (moderate risk). These updated guidelines emphasized the importance of the decision regarding timing of prophylactic thyroidectomy be based on direct DNA analysis in association with basal or stimulated serum calcitonin level. Children in the ATA-H category should have a thyroidectomy at or before 5 years of age, with the timing and extent of surgery guided by serum calcitonin levels. Children in the ATA-MOD category should undergo a thyroidectomy in childhood or young adulthood, of which the timing should again depend primarily on serum calcitonin levels.[10]

A retrospective review of outcomes of prophylactic thyroidectomy in children with MEN2 treated between 1995 and 2013 in the UK was published in 2018 and advocated for personalization of treatment based on the experience of the operating surgeon and patient factors over guidelines and recommendations in certain circumstances.[15] The majority of patients in this landmark paper were not treated in line with the ATA guidelines, yet the 8-year follow-up data did not show any convincing negative oncological outcomes. Ultimately, the authors recommended that genetic testing be undertaken as soon as possible to ensure that a truly prophylactic thyroidectomy is performed in a timely manner in children with MEN2A, such that the window of opportunity for cure of MTC is not lost. Some of the publications in the recent decade, and their recommendations, have been summarized in Table 29.1.

Table 29.1 Recent publications from around the world on management of the thyroid in MEN2 patients

Reference, Country	Study Design	Patient Cohort	Intervention	Main Findings	Recommendations
Ordóñez J et al. (2021)[16] Spain	Retrospective	30 patients (29 MEN2A and 1 MEN2B) treated between 2000 and 2019, with a mean age at surgery time of 7.0 ± 3.2 years and mean follow-up of 51 months	Total thyroidectomy without central neck dissection unless there was evidence of extended disease (elevated calcitonin or neck ultrasound)	• Age at surgery was the most important factor for malignant histopathology • Calcitonin levels were related to the progression of disease • Low rate of intraoperative and long-term complications when surgery is performed by highly specialized, albeit low-volume, surgeons	Patients with suspected or confirmed MEN2A syndrome should undergo a genetic analysis and measurement of the calcitonin and PTH serum levels before the fifth year of life in order for prophylactic surgery to occur before the recommended age.
Grubbs E et al. (2020)[17] USA	Retrospective prospective	18 patients with $C^{634}G$ mutation operated between 1972 and 1994 Median age at surgery was 15.5 years, with median follow-up time of 40 years	Total thyroidectomy and central neck dissection	• 83% (15/18) of children and young adults who underwent prophylactic thyroidectomy were free of disease at a median follow-up time of 40 years.	The earlier the age of a complete thyroidectomy, the higher the probability of a lifetime surgical cure.
Matsushita R et al. (2019)[18] Japan	Retrospective	21 patients (16 MEN2A, 5 MEN2B) <20 years diagnosed with germline *RET* mutations between 1997 and 2017	Total thyroidectomy alone, total thyroidectomy with central neck dissection, or total thyroidectomy with central and lateral neck dissection	• Mean disease onset possibility was at 5 years of age in ATA high-risk patients. The cumulative incidence of pathological onset or first calcitonin elevation timing reached 50% at 5 years and 100% at 9 years. • The cumulative incidence of pathological onset or first calcitonin rise in ATA moderate-risk patients reached 50% at age 8 years and 100% at age 17 years. • The incidence of permanent complications increased with age and as the area of the neck lymphadenectomy widened.	Prophylactic thyroidectomy reduces recurrence and postoperative complications in pediatric patients with MEN2. Early thyroidectomy based on only calcitonin level could possibly reduce thyroidectomy delay.

(Continued)

Table 29.1 (Continued) Recent publications from around the world on management of the thyroid in MEN2 patients

Reference, Country	Study Design	Patient Cohort	Intervention	Main Findings	Recommendations
Prete et al. (2018) UK[15]	Retrospective	79 MEN2 patients, <16 years who underwent DNA-directed thyroidectomy between 1995 and 2013. Median age of children at genetic testing was 4.3 years and 6.2 years for those undergoing surgery, with a median follow-up of 104.5 months.	Total thyroidectomy alone, total thyroidectomy with central neck dissection, or total thyroidectomy with central and lateral neck dissection	• 46% of patients had an operation performed above the age recommended by the ATA 2009 guidelines, and 38% had MTC on pathology. • Late surgery, above-normal preoperative calcitonin level, and MTC on pathology correlated with late genetic testing. • 32% of children had lymphadenectomy – complications relating to calcium control were higher in this group compared with those who underwent total thyroidectomy alone.	Early genetic testing and age-appropriate surgery may help avoid unnecessary lymphadenectomy and improve outcomes.
Bussières V et al. (2018)[19] Canada	Retrospective	21 MEN2 patients <18 years who underwent prophylactic thyroidectomy between 2006 and 2015. Mean age at surgery was 6.2 years, with a mean duration of follow-up of 4.1 years.	Total thyroidectomy *without* lymph node dissection	• 9 cases (43%) had microcarcinoma, while the other 12 cases had C-cell hyperplasia. Eight of these 9 cases were ATA high-risk. • Two patients had calcitonin >40 pg/mL, operated at 2 and 5 years of age, and were followed for 5.4 and 6.5 years, respectively. • There was no recurrence or persistent disease during the follow-up period.	The need for central neck dissection at the time of prophylactic thyroidectomy should be evaluated in a multi-institutional prospective manner, but it may be reasonable to omit it in patients younger than 10 years old unless calcitonin levels are remarkedly elevated.

(Continued)

Table 29.1 (Continued) Recent publications from around the world on management of the thyroid in MEN2 patients

Reference, Country	Study Design	Patient Cohort	Intervention	Main Findings	Recommendations
Opsahl et al. (2016)[20] Norway	Retrospective	60 of 67 Norwegian MEN2A patients who had thyroid surgery between 1974 and February 2015, with a median follow-up of 9.9 years.	Total thyroidectomy with or without lymph node surgery	• All patients with lymph node metastases had preoperative basal calcitonin levels ≥68 pg/mL. • All patients without central lymph node dissection and preoperative basal calcitonin <40 pg/mL were biochemically cured.	Preoperative basal calcitonin is the main guiding factor for optimal timing and extent of thyroid surgery. Under close observation, surgery can be postponed if basal serum calcitonin levels are normal.
Kluijfhout W et al. (2015)[21] The Netherlands	Retrospective	44 MEN2 patients (41 MEN2A, 3 MEN2B) younger than 17 years, with mean age of 5.7 years at time of surgery and median follow-up of 10.5 years.	Total thyroidectomy (only two patients had additional central neck dissection, as they exceeded the appropriate age for surgery)	• Higher incidence of hypocalcemia was seen with decreasing age at surgery (ns). • LOS was 6.7 days for patients <3 years vs. 1.7 and 3.5 days for patients aged 3–6 and those >6 years, respectively.	Total thyroidectomy should not be performed before the age of 3 for patients defined high risk by the ATA guidelines due to the higher rate of complications.

Note: ns, Nonsignificant.

In recent decades, prophylactic surgery has been offered to people who are at high risk for developing cancer. Examples of operating on an organ/gland that shows no signs of cancer in an attempt to prevent development of cancer of that organ/gland include correction of cryptorchidism or undescended testis, which is associated with a 10- to 40-fold increase in the incidence of testicular cancer; prophylactic colectomy for individuals susceptible to hereditary nonpolyposis colorectal cancer (HNPCC); and prophylactic mastectomy or oophorectomy for carriers of *BRCA1/2* gene mutations.

The landmark paper reviewed in this chapter presented the first data to help counsel patients with known *RET* gene mutations to consider surgery for their children at an early age with the expectation that the timing of surgical intervention would precede, and prevent, the development of MTC.

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Chapter 30

Pediatric Differentiated Carcinoma

Review by Frances T. Lee, Xavier M. Keutgen, and Peter Angelos

Landmark Paper

LONG-TERM OUTCOME IN 215 CHILDREN AND ADOLESCENTS WITH PAPILLARY THYROID CANCER TREATED DURING 1940 THROUGH 2008

Hay ID, Gonzalez-Losada T, Reinalda MS, Honetschlager JA, Richards ML, Thompson GB. *World J Surg.* 2010;34:1192–1202. doi: 10.1007/s00268-009-0364-0

RESEARCH QUESTION/OBJECTIVES

The management of pediatric differentiated thyroid cancer (DTC) has been difficult to standardize due to its rarity and significant clinical and biological differences from the adult disease. Importantly, among these differences is the superior survival seen in pediatric DTC patients despite a higher incidence of regional and distant metastatic disease at presentation. While surgery and adjuvant radioactive iodine (RAI) aim to eliminate disease and prevent recurrence, the optimal extent of surgical resection and decision to give RAI has not been clearly delineated. The lack of practice guidelines for pediatric DTC, in addition to emerging concerns regarding overtreatment and its potential negative sequelae, inspired the authors of this landmark paper to report their own evolved, long-term institutional experience and comparative outcomes in the management of pediatric DTC patients.

STUDY DESIGN

A retrospective review of pediatric patients diagnosed with papillary thyroid carcinoma (PTC) who underwent definitive primary surgical therapy at the Mayo Clinic from 1940 to 2008 (68-year period) was performed. Survivors were contacted and consented to provide postoperative follow-up data, and death certificates of deceased patients were also examined.

SAMPLE SIZE

Two hundred and fifteen PTC pediatric patients between 3 and 20 years of age.

INCLUSION/EXCLUSION CRITERIA

All patients under 21 years of age who underwent primary surgical therapy for PTC during the defined time period were eligible for study inclusion (n = 218). Only patients

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who did not provide consent to participate in the long-term postoperative follow-up portion of the study were excluded ($n = 3$).

INTERVENTION OR TREATMENT RECEIVED

Pediatric PTC patients underwent either bilobar resection (BLR), which included near-total thyroidectomy (NTT), total thyroidectomy (TT), or subtotal thyroidectomy (SBT), or a unilateral lobectomy (UL). These procedures were carried out with or without nodal dissection. Selected patients received postoperative radiation therapies in the form of radium seed application, external beam radiation therapy, or RAI with I-131, depending on the available therapy during the study period. All-cause and disease-specific mortality, as well as the rates of secondary malignancy, were reported. Postoperative cancer recurrences were compared between 1) UL versus BLR and 2) surgery alone versus surgery with adjuvant RAI. Studies of recurrence were only carried out in patients (89%) who had complete tumor resection and no distant metastases discovered within 30 days of their initial surgery.

RESULTS

Among the pediatric PTC patients reviewed, the mean age at diagnosis was 16 years (range 3–20 years) and 71% of patients were female. Approximately 17% of patients had a history of prior head or neck irradiation. Median PTC size was 2.2 cm (range 0.1–9.5 cm). Twenty-nine percent of PTCs were multicentric and 18% were locally invasive into extrathyroidal tissues. Seventy-eight percent of patients had metastatic involvement of regional lymph nodes at the time of their initial surgery and 6% had distant metastases. Over 90% of patients were considered "low risk" as per various prognostic scoring systems.

Regarding surgical management, 87% of patients underwent a BLR (45% NTT, 38% TT, 5% SBT) while 12% had a UL. Most patients (93%) had complete tumor resection. For patients who had concomitant lymph node(s) removal (86%), the most common initial procedure was node picking; however, more formal neck dissections in the form of central neck dissections (19%), unilateral (13%), or bilateral (13%) modified radical neck dissections were performed after 1990. Postoperative RAI was given to 35% of patients with localized disease who underwent complete tumor resection with BLR.

The median follow-up for this study was 28.7 years (range 0.6–64.5 years). While there were no deaths due to PTC within the first 20 years postoperatively, two patients (0.9%) died from recurrent distant metastatic disease at 28 and 30 years after BLR. However, none of the patients who *initially* presented with distant metastatic disease died during the study period. Overall, the group reported a cause-specific survival of 98% at 50 years. In terms of disease recurrence, 32% of patients who underwent a curative resection experienced either a local or distal recurrence by 40 years postoperatively. Patients who underwent BLR had a significantly lower disease recurrence than UL patients both locally (6% vs. 35%) and regionally (13% vs. 60%) at 40 years postoperatively. Of the patients who underwent BLR with curative intent, the 20-year

recurrence rates at local, regional, and distant sites were 3%, 16%, and 6%, respectively. Postoperative RAI did not improve recurrence or mortality risk when compared to patients who had curative surgery alone. Among patients who died of non-thyroid second primary malignancies (NSPMs), 73% had received radiation therapy including RAI.

STUDY LIMITATIONS

This study only included cases of PTC and excluded follicular thyroid carcinoma (FTC), which makes up a small, but non-negligible, proportion of all DTC cases. Furthermore, the study is retrospective, from a single institution, and prone to selection and referral pattern bias. Due to the study being conducted over a lengthy time period, treatment plans, including the extent of surgery and the use of RAI, evolved and were not uniform among study participants. In particular, lymph node dissections were not standardized in early patients, and a significant amount of "node picking" took place before complete removal, or compartment dissection, of affected lymph node basins was formally recommended. While this implies that some patients may have received subtherapeutic care, it also raises questions about potentially confounding variables in comparing different groups of patients. Lastly, the patients chosen for this study may not accurately reflect the pediatric population, as it examined patients between 3 and 20 years of age, which excluded younger infants and toddlers, yet it included young adults, which have a different prognosis. Thus, there is a possibility of skewed outcomes, which cannot be ascertained without knowing the true makeup of the cohort (not reported).

STUDY IMPACT

Due to the rarity, distinct nature, and lack of long-term outcomes for pediatric DTC, there were no formal pediatric management guidelines established at the time of this study. Traditionally, most pediatric DTC patients were treated aggressively with total thyroidectomy and reflexive postoperative RAI to eliminate disease. However, concerns emerged about overtreatment and associated sequelae in this prognostically favorable patient population. Along with several other important studies, this paper contributed to the creation of the American Thyroid Association (ATA) Management Guidelines for Children with Thyroid Nodules and Differentiated Thyroid Cancer in 2015.[1] The primary impact of this article was its reported outcomes from a large cohort of patients over the *longest* study period reported for pediatric DTC, which was 68 years. Results of this study helped with the development an understanding of the incidence of disease recurrence and cause-specific mortality after various surgical treatments for pediatric PTC. First, this study confirmed that overall survival for pediatric PTC patients is excellent, as they noted a cause-specific mortality of only 2% at 40 years. Overall survival was 98% at 50 years across all pediatric patients regardless of initial disease extent (localized vs. distant metastases) or surgical extent (UL vs. BLR). Nonetheless, the authors did observe increased rates of *recurrence* in pediatric patients who underwent a UL in the early study period from 1940 to 1969, with a local recurrence rate of 35% at 40 years after treatment in comparison to 6% seen in those who underwent BLR. This was an important consideration in the 2015 ATA guidelines, which recommends total thyroidectomy for most pediatric PTC patients to achieve long-term recurrence-free survival.[1]

Importantly, the authors did *not* observe any reduction in disease recurrence with the use of postoperative adjuvant RAI therapy. Moreover, among the patients who died of NSPM, a significant proportion had undergone radiation treatment including RAI. While the study did not show causation of NSPM from RAI, their results supported a more selective use of RAI, as reflected in the current ATA guidelines, for high-risk pediatric patients, while limiting exposure and potential sequelae of RAI among patients with limited or surgically curable disease.

RELEVANT ADDITIONAL STUDIES

Due to the increased incidence of multifocal (65%) and bilateral (30%–40%) disease occurring in pediatric PTC, TT has been generally recommended to maximize surgical cure.[2–6] On the one hand, Cherella et al. recently noted that bilateral disease and multifocality did not necessarily correlate with locoregional involvement, as seen in up to 45% of patients with clinically negative lymph nodes.[7] On the other hand, various early studies have concordantly reported increased risk of disease recurrence occurring in patients who undergo more limited thyroid resections when compared to TT.[8–10] While TT may improve disease-free survival, overall survival remains excellent among pediatric PTC patients who undergo either UL or TT.[11,12]

The 2015 ATA pediatric DTC guidelines currently recommend TT for most patients diagnosed with PTC, while supporting UL primarily for FTC.[1] In contrast, the 2015 ATA adult guidelines accept UL as a reasonable surgical option for adults with low-risk PTC.[13]

As such, it has been difficult to reconcile the rationale for TT in pediatric patients who, despite having a higher likelihood of advanced disease, have a significantly better prognosis than adults.[2,14] To confound matters further, complication rates from thyroidectomy among pediatric patients have been reported to be higher than that of adults and impact younger children more significantly.[15,16] Consequently, there is a renewed interest in the role of UL for pediatric PTC treatment, with various studies reporting favorable overall *and* disease-free survival, even among patients with multifocal disease.[12,17–20] In fact, there has been significant increase in the rate of UL for pediatric DTC even *after* the 2015 ATA pediatric guidelines recommending TT were published.[21,22] Thus, there may be an upcoming role for UL in treating select, low-risk pediatric PTC patients. Importantly, many studies caution that younger, prepubertal children may have poorer outcomes than adolescents, which calls for more specific and stratified guidelines among age groups with different biological and clinical disease.[23–26]

Lastly, the use of RAI has become more selective for the treatment of pediatric DTC, with a recent study showing its diminishing use between 2000 and 2018.[27] While RAI may benefit pediatric patients with nonsurgically resectable residual disease or distant metastases, several retrospective studies have reported an association of RAI with an increased risk for second malignancies and mortality.[28–30] Given these risks, as well as other significant side effects on pediatric patients, there are continued efforts to optimize the precise use of RAI for only those patients in higher-risk groups. In summary, this landmark study was among the early studies that challenged the reflexive use of RAI,

while emphasizing the importance of a surgically eliminating PTC, for more favorable long-term outcomes in the pediatric population.

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Chapter 31

Epidemiology

Review by Brendan C. Stack Jr.

Landmark Paper

INCIDENCE AND PREVALENCE OF PRIMARY HYPERPARATHYROIDISM IN A RACIALLY MIXED POPULATION

Yeh MW, Ituarte PH, Zhou HC, Nishimoto S, Liu IL, Harari A, Haigh PI, Adams AL. *J Clin Endocrinol Metab.* 2013;98(3):1122–1129. doi: 10.1210/jc.2012-4022. Epub 2013 Feb 15. PMID: 23418315; PMCID: PMC3590475

RESEARCH QUESTION/OBJECTIVES

The objective of this paper was to examine the incidence and prevalence of primary hyperparathyroidism (pHPT) within a racially mixed population.[1] Prior studies had been very homogenous, mostly consisting of white populations.[2–9] This study was a descriptive analysis of data from 3.5 million Kaiser Permanente Southern California (KPSC) members representing 20% of the insured population in a Southern California region (Los Angeles metropolitan area, https://thrive.kaiserpermanente.org).

STUDY DESIGN

This was a retrospective study of data from KPSC members, representing 20% of the insured population in a Southern California region (Los Angeles metropolitan area), collected between 1995 and 2010. Patients were treated for pHPT in accordance with the local standard of care during the study period. Successfully treated patients' data was censored from the prevalence data in the years following their surgery, as were patients with normal calcium for any given calendar year, de-enrolment from KPSC, or death.[1]

Incidence was defined by the authors as the number of pHPT cases per year divided by the number of KPSC subscribers for that same year. Patient study enrollment year was determined based on the date of the initial hypercalcemia value. Prevalence rates were calculated by tracking laboratory values over time. As long as a given case continued to have a high serum calcium level, it was included as part of the annual prevalence of pHPT.[1]

SAMPLE SIZE

The total population of hypercalcemia with one elevated value was 57,132 patients. After exclusions, 40,857 patients were eligible for further analysis. A total of 15,234 patients were identified with chronic hypercalcemia, 13,327 (87%) of which had pHPT;

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6,868 of these patients had classic pHPT, 6,459 had nonclassic (borderline) pHPT, and 428 possible pHPT. A total of 27,530 patients had chronic hypercalcemia without parathyroid hormone (PTH) data available. Of these, 25,623 patients had no additional episodes of hypercalcemia within 3–24 months of their index result. A total of 1,479 patients with elevated calcium had non-pHPT explanations (malignancy or thiazide diuretic use).[1]

INCLUSION/EXCLUSION CRITERIA

Inclusion criteria was at least one calcium value greater than 10.5 mg/dL. Patients were later classified as classic pHPT (calcium greater than 10.5 mg/dL and PTH greater than 65 pg/mL/6.8 pmol/L), nonclassic pHPT (calcium greater than 10.5 mg/dL and inappropriately normal or nonsuppressed PTH 21–65 pg/mL), and possible pHPT (patients not meeting any of these criteria that were followed for a second high serum calcium level within 3–24 months to confirm chronic hypercalcemia). Patients with only a single high calcium level were considered spurious cases and were excluded.

Excluded patients were KPSC members for less than 6 months, age younger than 20 years, and those with a secondary or tertiary hyperparathyroidism diagnoses. Additional exclusions included a history of invasive cancer and those with a history of thiazide diuretic use at any time within 24 months of the index high calcium date. Those with documented low PTH values, less than 21 pg/mL, were also excluded.

INTERVENTION OR TREATMENT RECEIVED

This was an observational study; however, any hypercalcemic patients diagnosed with pHPT were managed in accordance with local standards. Those operated upon and cured were censored from the data in subsequent years.

RESULTS

The incidence of pHPT was consistently higher in women (mean 2.7/100,000), and this is consistent with current disease understanding. The African American patient subgroup had the highest rates of calcium testing, also women more than men, and this was a novel finding. The incidence of pHPT increased with advancing age, with age-adjusted incidence also being greatest among African Americans. Age-adjusted prevalence increased from 76.2 to 232.7/100,000 among African American women and 29.5 to 85.2/100,000 among African American men, which was almost entirely attributable to an increase in cases of the classic variant of pHPT.

Primary HPT was most prevalent among older African Americans, women between 70 and 79 years old, and men over 80 years. Its average peak prevalence was 921.5/100,000 (vs. age-matched whites at 630.3, $p < 0.0001$) and 481.1/100,000 (vs. age-matched whites at 164.7, $p < 0.0001$) for women and men, respectively. Ultimately, the highest prevalence for any age or racial group was 1,408.9/100,000 for African American women during the final year of the study (2010).

Secondarily, this chapter confirms that pHPT is the leading cause of hypercalcemia. This information, when taken along with an understanding that in contemporary medical

practice up to 75% of hypercalcemia goes unrecognized or untreated,[10–13] makes a compelling argument that a large reservoir of untreated pHPT exists.

STUDY LIMITATIONS

The incidence and prevalence values may have been underestimated by virtue of excluding patients with chronic kidney disease, patients on thiazide diuretics, and invasive cancer patients, all of whom may have had concurrent pHPT as a contributor to hypercalcemia. Data in the possible pHPT group may have been contaminated with patients with non-pHPT hypercalcemia such as those with hypervitaminosis D, milk alkali syndrome, hyperthyroidism, familial hypocalciuric hypercalcemia (FHH), and sarcoidosis.[1,11]

STUDY IMPACT

This landmark paper was the first to study pHPT incidence/prevalence in a mixed racial population. By doing so, it revealed instructive data about racial differences regarding pHPT. These racial differences may increase provider recognition of the clinical significance of hypercalcemia among racial subgroups. The chief message from this article is that pHPT is increasing in incidence among all ages and genders. Its incidence also does have some distinctions when examined specific to the racial background of the patient. Increases in prevalence estimation may be confounded if nondiagnosed and nonoperated patients accumulated in the study population over time.

Patients of African descent have demonstrated greater increase in pHPT compared to other racial groups. This paper has set the stage for further research, namely why are these increases happening?

Is pHPT epidemiology truly changing, or are study observations a reflection of an evolution in its clinical behavior and/or a proliferation of testing? The proportion of patients with at least one serum calcium level drawn per year increased from 6.8% in 1995 to 12.7% in 2010 and from 5.3% to 8.9% for women and men, respectively. This increase did not correlate with the incidences of pHPT in the population for either sex. This warrants further examination over a longer period or in another population sample. Secondarily, this article confirms that pHPT is the leading cause of hypercalcemia. This information, when taken along with the knowledge that in contemporary medical practice up to 75% of hypercalcemia cases go unrecognized or untreated,[10–13] makes a compelling argument that a large reservoir of untreated pHPT exists.

The effects of observed or untreated hyperparathyroidism are known.[14] This landmark paper shows that a large population of patients exists with undiagnosed and untreated pHPT, particularly among black, but also white populations. It is reasonable to conclude that significant morbidity could be prevented by increased awareness and treatment of this disease. Several recommendations for clinical practice can be made based on this landmark paper's findings, including increased awareness of hypercalcemia and its causes, education for healthcare professionals about the cause of hypercalcemia (especially pHPT), an explanation of how the pHPT diagnosis is made, and

encouragement for the referral of patients with confirmed hypercalcemia to specialists and centers with high-volume experience in treating pHPT.

RELEVANT ADDITIONAL STUDIES

Calcium testing became a diagnostic tool for detecting hyperparathyroidism, and the test's proliferation as part of a serum multianalysis laboratory panel increased in the 1970s. Unfortunately, most physicians forget about pHPT and its relationship with hypercalcemia, and its neglect has become an obstacle to making a timely diagnosis.

Other groups have since noted Yeh's findings of an increase in pHPT in diverse racial populations and from different geographies.[5–9, 15–18] Additionally, many have recently noted that hypercalcemia has widely gone underappreciated, even after testing, despite being present in the electronic medical record.[10–13] A systematic electronic medical record review taken by the investigators noted earlier was a similar approach taken by Yeh et al. to identify their study population.[1]

Patients with chronically undiagnosed pHPT experienced progression of the sequelae of their disease and of delayed surgical referral,[19] and this could be addressed through raising awareness/education of the morbidity associated with pHPT among healthcare professionals.[20,21] pHPT has been reported to have an increasing incidence.[22] This increase appears across all racial and age categories and geographies. Thought by some to be a consequence of increased testing for calcium, there appears to be other factors which may explain the increased incidence.[22–24]

Attention should be paid to hypercalcemia, and it should be confirmed and evaluated in a timely manner.[14,23,24] This landmark study adds to current knowledge of the diversity of patients with hypercalcemia that are subsequently diagnosed with pHPT. Future research should examine risk factors for this "idiopathic" disorder, which might explain its changing incidence/prevalence.[21,25] These risk factors may be unique to given racial groups. When identified, this understanding may create an opportunity for education and intervention for this condition.

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Chapter 32

Natural History of Untreated Disease

Review by Fares Benmiloud

Landmark Paper

A 10-YEAR PROSPECTIVE STUDY OF PRIMARY HYPERPARATHYROIDISM WITH OR WITHOUT PARATHYROID SURGERY

Silverberg SJ, Shane E, Jacobs TP, Siris E, Bilezikian JP. *N Engl J Med.* 1999;341(17): 1249–1255. doi: 10.1056/NEJM199910213411701

RESEARCH QUESTION/OBJECTIVES

Due to the heterogeneous and nonspecific clinical presentation of parathyroid pathology at diagnosis, the question of the objective benefit of surgery, particularly in asymptomatic patients, arose in the early 1990s at the National Institutes of Health (NIH) Consensus Development Conference on the Diagnosis and Management of Asymptomatic Primary Hyperparathyroidism. The aim of this prospective landmark paper was to describe the natural history of primary hyperparathyroidism, comparing the biochemical, osteodensitometric, and histomorphometric evolution of disease at 10 years in patients operated on for primary hyperparathyroidism to those followed without surgery. The main study aim was to compare the clinical course and development of complications in each of the following groups: the group of patients ($n = 61$) who had undergone parathyroidectomy and those ($n = 60$) who were not operated on.

STUDY DESIGN

This was a prospective single-center study that analyzed a cohort of primary hyperparathyroid patients followed over a 10-year period. Patients were followed up every 4–6 months by biological assessment (calcium, phosphorus, alkaline phosphatase, parathormone, 25-hydroxyvitamin D and 1,25-dihydroxy- vitamin D, osteocalcin, urinary pyridinoline and deoxypyridinoline, urinary calcium) and bone mineral density (BMD) every year by absorptiometry at the lumbar spine, femoral neck, and distal radius.

SAMPLE SIZE

The study enrolled 137 patients over a 7-year period, and the 121 patients who followed the monitoring protocol for at least 1 year were included in the final analysis.

DOI: 10.1201/9781003196211-32

INCLUSION/EXCLUSION CRITERIA

The study included primary hyperparathyroid patients, defined as hypercalcemia associated with high serum parathyroid hormone. Patients receiving thiazide or lithium were excluded.

INTERVENTION OR TREATMENT RECEIVED

The intervention assessed was parathyroidectomy. The indications for parathyroidectomy were either symptoms, or for asymptomatic patients, the criteria were defined in the guidelines of the NIH Consensus Conference in 1991.[1] Symptoms of hyperparathyroidism were osteitis fibrosa cystica, nephrolithiasis or nephrocalcinosis, neuromuscular objective symptoms (like proximal muscle weakness, atrophy, hyperreflexia, and gait disturbances), and/or hyperparathyroid crisis. Patients with nonspecific symptoms often associated with hyperparathyroidism, such as fatigue, weakness, and constipation, were considered asymptomatic. Indications for parathyroidectomy in asymptomatic patients were one or more of the following: serum calcium >3 mmol/L, urinary calcium >400 mg or 10 mmol/day, reduced bone cortical density (z-score < –2 for the radius), unexplained mild renal failure, and age <50 years.

RESULTS

Of the 121 patients included in the final study population (30 men and 91 women, age range from 20 to 79 years), only 20 patients (17%) were symptomatic. Symptoms were primarily urinary (kidney stones), as there was no clinical bone disease, fracture, neuromuscular symptoms, or episodes of hyperparathyroid crisis. The two groups of patients were slightly different at baseline: operated patients were younger and had higher serum calcium concentrations, urinary calcium excretion, and lower vertebral and femoral z-scores than patients who were only followed clinically. BMD at the radius, serum parathyroid hormone, alkaline phosphatase, and vitamin D levels were similar between the two groups.

Parathyroidectomy led to biochemical cure in all operated patients. It resulted in a mean increase in BMD of the femoral neck of 6% of patients after 1 year ($p = 0.002$) and 14% after 10 years ($p = 0.002$), and that increase was significantly sustained from postoperative year 1 to postoperative year 10. Lumbar spine BMD increased by 8% after 1 year ($p = 0.005$) and 12% after 10 years ($p = 0.03$). BMD of the lumbar spine and femoral neck increased comparably in postmenopausal operated women, as in premenopausal women and men, and it increased similarly in symptomatic and asymptomatic patients. There was no significant change in BMD of the radius. Overall, the 52 asymptomatic patients who did not undergo surgery had no significant change in their serum calcium, parathyroid hormone, alkaline phosphatase, urinary calcium excretion, or BMD over the 10-year period. However, 11 of these 52 patients (21%), mostly women, had a decrease of >10% in BMD, and 14 patients (27%) developed at least one new indication for surgery: marked hypercalcemia ($n = 2$), marked hypercalciuria ($n = 8$), and low cortical BMD ($n = 6$). Among the 20 symptomatic patients, who all had kidney stones, none of the 12 who

underwent surgery had recurrent kidney stones, whereas 6 of the 8 patients who did not undergo surgery did have a recurrence.

STUDY LIMITATIONS

This is a single-center observational study, which focuses on the bone impact and symptomatic renal stones. It does not include other relevant potential benefits of the treatment of primary hyperparathyroidism, such as renal function, occurrence of nephrocalcinosis, cardiovascular events, neuropsychic disorders, quality of life, or cost-effectiveness of treatment. Another limitation would be the lack of information provided in this study regarding the surgical treatment arm, which is important for decision-making in this disease.

STUDY IMPACT

This study was the first report to prospectively provide a long-term answer (with 10 years of follow-up) to a simple and critical question, that of the potential benefit of operating on patients diagnosed with primary hyperparathyroidism, compared to simple monitoring. It confirmed preliminary results from the same cohort,[2] which had noted 5 years previously, a normalization of biochemical values and an increase in BMD at the lumbar spine and femoral neck. The observations made in this study also helped to identify patients in whom surgery was beneficial: those with symptomatic urolithiasis, for whom surgery could help prevent stone recurrence, and those with low BMD at diagnosis, who could expect an improvement in this density in cancellous bone after surgery.

On the other hand, the study raises interesting unresolved questions regarding bone pathophysiology in patients diagnosed with primary hyperparathyroidism, whose cancellous bone density, although lower than in normal subjects, remains stable over time, whereas physiologically, it decreases over time in normal subjects.

RELEVANT ADDITIONAL STUDIES

The beneficial effects of parathyroidectomy on bone, by decreasing the porosity of cortical bone and increasing the density of cancellous bone, has been confirmed by other groups, including two randomized studies,[3,4] and in an updated study performed by the same group 5 years later.[5] That study showed that the positive effect on BMD continued to be significant 15 years after parathyroidectomy, since patients who were not operated on had a BMD decline of 10% and 35% at the femoral neck and distal radius, respectively.[5] This improvement appeared to be related to the quantity (BMD) and quality of the bone (microarchitecture).[6] Also, subsequent studies have shown the benefits of parathyroidectomy in reducing fracture rates.[7–9]

Similarly, several studies have confirmed a positive effect of parathyroidectomy on the kidney, mainly through a marked reduction in the development of kidney stones.[10,11] Mollerup et al, in a multicenter, controlled, retrospective follow-up study, found that the

incidence rate ratio of stone episodes of patients who had primary hyperparathyroidism, as compared to normoparathyroid control patients, decreased from 40.6 before parathyroid surgery to 16.9 after surgery ($p < 0.01$). They also found that the risk of a stone episode, which was increased preoperatively, normalized more than 10 years after surgery. Similarly, Deacoson et al., in a follow-up registry study, found that the risk of stone episodes decreased significantly from 0.36 per patient per year preoperatively to 0.02 per patient per year postoperatively ($p < 0.001$). Other studies have provided evidence of the impact of parathyroid surgery on renal function[12,13]: Hedback et al. reported a 28% increase of renal concentration capacity, soon after surgery, while Tassone et al. reported a significant improvement of renal function (estimated glomerular filtration rate [GFR]) in operated patients who had concomitant renal disease and an estimated GFR less than 60 mL/min/1.73 m^2 ($P < 0.0002$).

The literature has also evaluated the cardiac benefits of parathyroidectomy. Indeed, surgery has not only been shown to improve left ventricular diastolic function, cardiac irritability, and ST subequalization at 5 years postoperatively, but also left ventricular mass, systolic and diastolic function, and vasodilation at 6 months postoperatively.[14,15]

Finally, the effect of parathyroidectomy on neuropsychological signs related to hyperparathyroidism has been the subject of numerous studies, which showed rapid and sustained improvement in signs of anxiety and depression, as well as in the memory of operated patients.[3,16,17] Ambrogini et al., in a prospective randomized study, showed significantly better scores of quality of life (SF-36), psychosocial well-being (SCL-90R), and emotional role function in the operated compared with the nonoperated patients ($P = 0.027$), while Pasieka et al. showed an improvement in symptoms related to the parathyroid disease after parathyroid surgery, though significant only during the first postoperative week, and a perception of 60% increase in general health at 1 year postoperatively.

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Chapter 33

Surgical Indications

Review by Peter Truran

Landmark Paper

RANDOMIZED CONTROLLED CLINICAL TRIAL OF SURGERY VERSUS NO SURGERY IN PATIENTS WITH MILD ASYMPTOMATIC PRIMARY HYPERPARATHYROIDISM

Rao DR, Phillips ER, Divine GW, Talpos GB. *J Clin Endocrinol Metab.* 2004;89(11): 5415–5422. doi: 10.1210/jc.2004-0028

RESEARCH QUESTION/OBJECTIVES

Current guidelines recommend parathyroidectomy for patients with primary hyperparathyroidism with symptoms, under 50 years old, or evidence of end-organ effects (osteoporosis, osteoporotic fracture, nephrolithiasis, reduced creatinine clearance).[1] The role of parathyroidectomy in asymptomatic patients without these features is debated. The aim of this landmark paper was to determine if parathyroidectomy improves quality of life or bone mineral density (BMD) in patients who did not meet the criteria for surgery based on the published guidelines.[2]

STUDY DESIGN

Prospective randomized controlled trial (RCT) of parathyroidectomy versus observation in patients with asymptomatic primary hyperparathyroidism.

SAMPLE SIZE

Patients were identified from referrals or laboratory computer tracking for hypercalcemia between 1994 and 1997 at the Henry Ford Health System. Fifty-three asymptomatic primary hyperparathyroid patients were randomly assigned to either undergo parathyroidectomy ($n = 25$) or observation ($n = 28$). Twenty-three of the 25 patients randomized to surgery underwent their operation within 3 months. Three of the 28 patients randomized to observation underwent surgery within 1 year. Results were analyzed on an intention-to-treat basis.

DOI: 10.1201/9781003196211-33

INCLUSION/EXCLUSION CRITERIA

Patients with asymptomatic primary hyperparathyroidism who did not meet any of the criteria for parathyroidectomy according to the 2002 National Institutes of Health Consensus Guidelines at the time were excluded.[2] The study inclusion criteria were:

- Age: 50–75 years
- Adjusted calcium: 10.1 and 11.5 mg/dL (2.52–2.87 mmol/L)
- Parathyroid hormone (PTH) level >20 pg/mL
- Normal renal function, defined as serum creatinine less than 1.5 mg/dL (133 mol/L)
- Forearm BMD within 2 standard deviations (SD) adjusted (z-scores)
- Absence of relevant symptoms of primary hyperparathyroidism

Patients were excluded if they had a history of familial hyperparathyroidism, previous neck surgery or current thyroid disease requiring surgical intervention, nontraumatic vertebral or hip fractures, or nephrolithiasis within the past 2 years. Also excluded were women within 5 years of menopause and patients taking medications known to affect bone and mineral metabolism.

INTERVENTION OR TREATMENT RECEIVED

Following randomization patients were followed up for at least 24 months. Four-gland parathyroid exploration was undertaken within 3 months of randomization in the surgery group. Surgery was undertaken by a single experienced surgeon but without localization scans. Patients were seen every 6 months following randomization and assessed for symptoms of hypercalcemia and complications of hyperparathyroidism. Biochemical assessment, including serum calcium, ionized calcium, PTH, renal function and alkaline phosphatase, was measured. Quality of life (QoL) was assessed using the SF-36 standardized, validated questionnaire and bone density with a dual energy x-ray absorptiometry (DEXA) scan every 6 months. Psychological disturbance was assessed yearly using the Symptom Checklist revised (SCL-90R), a validated tool for measuring mental health status in nine domains.

RESULTS

Following surgery there were expected falls in the serum calcium, PTH, bone-specific alkaline phosphatase, and 24-hour urine calcium. There was no change in the renal function in either group over the study period, and the biochemical indices of disease severity and bone turnover likewise did not change with time in the observation group.

Compared to the observation group, this study noted a significant increase in BMD following parathyroidectomy at the femoral neck and total hip (a group difference of 0.8%/year; $p = 0.01$ and 1.0%/year; $p = 0.001$, respectively) and a nonsignificant improvement in the BMD of the spine and forearm (a group difference of 0.6%/year and 0.2%/year).

QoL was significantly better in two of the nine domains, social function and emotional role, measured by the SF-36, in the surgical compared to the observational group. (p = 0.007 and 0.012, respectively). In the observation group there were significant declines in 5 of the 9 domains (social, physical, emotional, energy, and health perception), whereas in the surgical group only one domain declined significantly (physical).

Two of the nine psychological domains, anxiety and phobia, were significantly improved following surgery in comparison to the observational group in SCL-90R. But none of the psychological domains deteriorated in the observational group over the study period.

Three patients in the surgical group developed recurrent disease. One patient in the observation group developed kidney stones, one had an episode of pancreatitis, and another developed significant symptoms of hyperparathyroidism. All three of these patients underwent parathyroidectomy.

STUDY LIMITATIONS

This study was relatively small with a follow-up period of only 2 years. A greater number of patients and longer follow-up of bone outcomes and QoL would provide more robust evidence to support the conclusions. The study included patients who were "asymptomatic," but it was not defined which symptoms were used for this assessment or exactly how patients were diagnosed.

There were 283 patients eligible for the study, and 95 (33%) refused surgery. There may have been a selection bias in the study for patients who had low-grade symptoms. In addition, some of the improvement in QoL may be explained by a placebo effect of surgery. A single experienced surgeon performed the bilateral parathyroid surgery, and all patients were between 50 and 75 years old. It is not clear that the findings can be generalized to other surgeons, other operating techniques, or older or younger patients.

Although the study showed a statistically significant improvement in BMD at 2 years in the parathyroidectomy group, it is not clear that this was actually clinically significant. The authors recognize that a larger study with a longer follow-up would be required to assess the effect of parathyroidectomy on nephrolithiasis, fractures, morbidity, and mortality.

STUDY IMPACT

This study was the first RCT to show a potential benefit of surgery in asymptomatic patients who did not yet meet the accepted criteria for parathyroidectomy. Furthermore, this study demonstrated that a surgical RCT was feasible in this area, and since this study, three other RCTs have been published.[3–5] Although the guidelines[2] did not change after this study was published (Table 33.1), subsequent guidelines (2009 and onwards) recognized that parathyroidectomy *may* be of benefit to all asymptomatic patients.[1,6,7]

Recent UK guidelines also have recognized this. The latest National Institute Clinical Excellence (NICE) guidelines recommend that all patients with asymptomatic primary hyperparathyroidism have a discussion with their physician about the potential benefits

Table 33.1 Current and previous NIH guidelines for the management of asymptomatic primary hyperparathyroidism

Variable	2002[2]	2009[6]	2014[7]
Age	Under 50 years	Under 50 years	Under 50 years
Bone Disease	DEXA T score < −2.5 any site	DEXA T score < −2.5 any site Osteoporotic fracture	DEXA T score < −2.5 any site Osteoporotic fracture
Renal Disease	24-hr urine calcium >400 mg Cr clearance reduced by 30%	Cr clearance <60 cc/min	Cr clearance <60 cc/min 24-hr urine calcium >400 mg
Serum Calcium	1.0 mg/dL (0.25 mm/L) above normal	1.0 mg/dL (0.25 mm/L) above normal	1.0 mg/dL (0.25 mm/L) above normal

Abbreviations: DEXA, dual energy x-ray absorptiometry; Cr, creatinine.

of surgery.[8] This landmark RCT importantly led to the idea that there are not necessarily any disease-specific *contraindications* to surgery.

RELEVANT ADDITIONAL STUDIES

Subsequent to this landmark paper, a similar randomized study of 191 patients with a follow-up of 5 years was conducted that again demonstrated the positive effect of parathyroidectomy on bone density and QoL.[5] However, the 10-year outcomes from the same study found no significant differences in QoL and no significant differences in clinical outcomes.[9,10] The authors concluded that parathyroidectomy does not reduce morbidity or mortality in mild primary hyperparathyroidism cases compared with observation. The study found no significant differences with respect to mortality, fractures, cancer, cardiovascular and cerebrovascular events, or renal morbidities.[10]

A U.S. population-based study of 210,206 patients with primary hyperparathyroidism (mean age 75, 30% underwent parathyroidectomy) found that parathyroidectomy significantly reduced fracture risk in the multivariable analysis. The study found that at 2, 5, and 10 years, parathyroidectomy was associated with adjusted absolute fracture risk reduction of 1.2% and 5.1%, respectively, compared with nonoperative management.[11]

A systematic review and metanalysis published in 2020 of four RCTs (229 patients in total) that met their inclusion criteria (including this landmark paper) found that patients with mild asymptomatic disease had an improvement in BMD after parathyroidectomy compared with observation. Their conclusion was that there was not currently enough available evidence from randomized studies to confirm a benefit in terms of QoL or reduced fracture risk.[12]

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CHAPTER 34

Preoperative Localization

Reviewed by Saba P. Balasubramanian

Landmark Paper

OPERATION FOR PRIMARY HYPERPARATHYROIDISM: THE NEW VERSUS THE OLD ORDER. A RANDOMISED CONTROLLED TRIAL OF PREOPERATIVE LOCALISATION

Aarum S, Nordenström E, Reihnér J, Zedenius H, Jacobsson R, Danielsson M, Bäckdahl H, Lindholm G, Wallin B, Hamberger lOF. *Sc and J Surg.* 2007;96(1):26–30. doi: 10.1177/145749690709600105

RESEARCH QUESTION/OBJECTIVES

This landmark paper by Aarum et al.[1] aimed to evaluate the effectiveness and cost of preoperative localization scans (with sestamibi scan ± ultrasound) prior to first-time surgery performed for the treatment of primary hyperparathyroidism (PHPT). The primary research question was: "What was the effect of preoperative imaging on operative strategy and rates of postoperative normocalcemia?" A secondary question was related to the costs of patient treatment with and without preoperative localization.

STUDY DESIGN

The study was a pragmatic, open, single-center, two-arm controlled trial in which patients undergoing first-time surgery for PHPT were randomly allocated to either undergo preoperative imaging (group I) or not (group II). The results of preoperative imaging (group I) dictated whether a focused/unilateral operation was performed, while all patients in group II underwent a bilateral neck exploration (BNE).

INCLUSION/EXCLUSION CRITERIA

Only patients older than 50 years undergoing first-time surgery for PHPT were considered for inclusion. Patients with a genetic predisposition, concomitant large goiter, and those not suitable for day surgery were excluded.

SAMPLE SIZE

Interestingly, sample size calculations were not done to test the null hypothesis of "no difference" in normocalcemia rates between the two arms. The authors argued that a randomized controlled trial (RCT) to evaluate differences in the primary outcome would not be feasible given the small expected difference (effect size) in normocalcemia rates,

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based on results from their institution. Instead, they justified a much smaller sample size of 100 patients by describing this article as a feasibility study.

INTERVENTION OR TREATMENT RECEIVED

Patients in group I initially underwent a sestamibi scan, and if this localized a possible pathological parathyroid gland, an ultrasound was performed. For patients in which the scans were concordant and showed a single abnormality on one side, an open unilateral operation was performed. For other patients in group I and those in group II, a BNE was undertaken. The primary outcome was normocalcemia at 6 months.

RESULTS

In group I, 23/50 (46%) patients underwent unilateral surgery based on preoperative imaging. The normocalcemia rates at 6 months post-operatively were 96% and 94% in groups I and II, respectively, and this difference was not statistically significant. The median (range) operative times in groups I and II were similar: 50 (14–145) minutes and 60 (30–155) minutes, respectively. The median (range) length of neck incision was 53 (20–90) mm in group I and 65 (40–100) mm in group II; this was statistically significant ($p < 0.05$). Only a single patient (group I) had a transient recurrent laryngeal nerve paresis.

STUDY LIMITATIONS

The most important limitation of this study is the risk of a type II error in the absence of an appropriate sample size calculation that includes key parameters such as the primary outcome, effect size, and design (superiority vs. noninferiority). The authors have not provided clarity as to whether the preoperative imaging was intended to increase their success rates (superiority design) or to accrue other benefits without an impact on success rates or costs (noninferiority design). On this basis, the rationale that "a very large sample size" (without mention of the numbers needed) is not feasible is hard to justify.

The trial used a specific imaging protocol (use of ultrasound dependent on MIBI findings) that directs operative strategy. Numerous variations of localization methods (routine use of ultrasound, inclusion of other imaging modalities, and use of intraoperative aids) used in other centers, along with the stringent eligibility criteria, may affect the generalizability of the study findings. While the article has understandably focused on one important primary outcome (normocalcemia at 6 months postoperatively) and a few relevant secondary outcomes (including operating time, length of scar, and costs), other outcomes could have also been studied. These include potential delays in treatment and detection of incidentalomas, as use of imaging increases the risk of detection of incidentalomas in the thyroid, breast, and other organs in the upper body.[2] In addition, the potential for recurrence (as a long-term outcome) may have been higher in patients undergoing scan-directed parathyroidectomy, and this has (understandably) not been explored. While costs of treatment have been compared, this only relates to imaging and operating time; costs of treating persistent disease and potential for reduced hospital stay have not been considered. Intraoperative parathyroid hormone (PTH) testing (not used in

this study) is widely available and could have further impacted study results. The absence of postoperative hypocalcemia in the entire cohort may reflect an overall milder disease spectrum (and thereby reduced hungry-bone syndrome) and the preponderance of 'single gland' disease (resulting in less hypoparathyroidism); again, limiting external validity.

STUDY IMPACT

Preoperative imaging for PHPT was introduced into clinical practice over 20 years ago following the successful demonstration that enlarged parathyroid glands are often visible on ultrasound and nuclear medicine imaging. As with many surgical procedures, preoperative imaging became widely adopted without being subject to rigorous testing for clinical benefit in RCTs. Surgeons across the world started to routinely perform preoperative imaging[3] with the stated advantages of potentially avoiding a general anesthetic, reduced operating times, shorter hospital stay, reduced postoperative pain and discomfort, lower risk of hypocalcemia, and reduced incision size.[4] However, disadvantages such as cost of imaging (particularly with sestamibi scans), detection of incidental findings of little significance, exposure to radiation, and the potentially increased risk of persistent and/or recurrent disease were overlooked in the enthusiasm to adopt newer techniques. This study was the first reported RCT that addressed the effectiveness of preoperative imaging, and despite its limitations, it highlighted the lack of a clear and measurable benefit of preoperative imaging in patients with PHPT.

RELEVANT ADDITIONAL STUDIES

In addition to the attainment of normocalcemia, objectives of parathyroid surgery include avoiding or minimizing the risk of hypocalcemia and hypoparathyroidism, recurrent disease, recurrent laryngeal nerve injury, postoperative bleeding, and infection. The challenge in optimizing these outcomes lies in the ability to accurately locate abnormal glands and preserve normal parathyroid tissue with as little unnecessary dissection as possible. Preoperative imaging may help not only in localizing abnormal glands and provide surgeons with a roadmap, but also potentially limiting further dissection that may be unnecessary in patients with single-gland disease, which is the pathology in the vast majority of PHPT patients.[5] In addition, imaging may help detect the rare instance of the mediastinal or other ectopic gland(s) that are not accessible or detected during a neck exploration. The downsides of routinely employing imaging are the proportion of patients with negative imaging[1]; the potential for missed multigland disease, which is the most common cause of failure in first-time parathyroid surgery[6]; the detection of indolent incidental lesions[2]; and the potential contribution to imaging overuse, a common problem in modern medicine.[7] In the absence of strong evidence to show that preoperative imaging improves any of the clinical outcomes mentioned, it would be reasonable to assume that there is clinical equipoise on the effectiveness of preoperative imaging. In keeping with this, the American Association of Endocrine Surgeons guidelines[8] and the UK National Institute for Health and Care Excellence (NICE) guidelines (NG132) on PHPT do not mandate the use of preoperative imaging. However, they do make recommendations about the type of imaging and intraoperative techniques that may be useful.

In a related small RCT that aimed to compare focused surgery versus BNE,[9] preoperative imaging and (interestingly) intraoperative PTH estimations were only performed in the focused group. This study found similar cure rates and operating time in both groups, but lower pain, shorter scars, and better cosmesis in the focused group. It could be argued that this was despite the significant bias toward better outcomes in the focused group.

There are a few other studies (and no Cochrane reviews) that have specifically addressed this issue of preoperative imaging for parathyroidectomy. However, the question of focused/unilateral versus BNE has been addressed in several trials and by a systematic Cochrane review.[3] The issues may be similar, as the purpose of imaging is to facilitate focused surgery. However, the question of the optimal surgical strategy is a distinct one, and it relates not only to preoperative imaging but also to intraoperative aids. This topic is discussed further in other chapters in this book on landmark papers related to the operative approach.

Despite the limitations of this study, I consider this a landmark paper, as it aimed to provide the basis of level I evidence to address an important issue (the role of preoperative imaging) that is still relevant today. Clinicians (surgeons in particular) and radiologists usually tend to embrace technology based on a 'theoretical' rationale and adopt it into routine clinical practice prior to rigorous testing in good-quality clinical trials. While there are famous instances of interventions (such as laparoscopic cholecystectomy) that have withstood the test of time despite early good-quality RCTs not demonstrating significant benefit,[10] there are many more instances of technologies falling out of favor after much initial enthusiasm (i.e., the Scott's parabola).[11]

As with laparoscopic cholecystectomy, this article clearly has not stemmed the tide of preoperative imaging in PHPT that is currently part of standard clinical care in most centers. I am certainly not making the case for abandoning imaging in PHPT. However rare, most experienced parathyroid surgeons would have had the experience of detecting a mediastinal or an ectopic parathyroid on a preoperative scan and feeling grateful that they had not ventured into a neck exploration! At the same time, and probably much more commonly, surgeons wonder about the time and resources expended on preoperative imaging with its limited contribution to improving key clinical outcomes; not to mention, the additional burden of incidentaloma detection![2]

What I think this article does for us (and I hope for the next generation of surgeons) is highlight the importance of rigorous testing of new interventions and evaluation of both their potential benefit and harm. In addition, the growing use of intraoperative localization techniques such as radioguidance and fluorescent imaging and aids such as intraoperative PTH assays should lead us to look again at the contribution of Aarum and colleagues and wonder if it is time to put the localization technologies we use through the rigors of testing in randomized clinical trials.

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Chapter 35

Surgeon Volume

Review by Rongzhi Wang and Herbert Chen

Landmark Paper

OPERATIVE FAILURES AFTER PARATHYROIDECTOMY FOR HYPERPARATHYROIDISM: THE INFLUENCE OF SURGICAL VOLUME

Chen H, Wang TS, Yen TWF, Doffek K, Krzywda E, Schaefer S, Sippel RS, Wilson SD. *Ann Surg.* 2010;252(4):691–695. doi: 10.1097/SLA.0b013e3181f698df

RESEARCH QUESTION/OBJECTIVES

First-time parathyroidectomy for primary hyperparathyroidism (pHPT) has a >95% cure rate, but a small minority of patients develop persistent/recurrent hyperparathyroidism requiring reoperation. pHPT is considered persistent if the total serum calcium level is elevated above normal at the 6-month postoperative mark, while recurrent pHPT is defined as a new elevated total serum calcium level, after a normocalcemic interval, at more than 6 months postoperatively. Reoperative parathyroidectomy is associated with an increased risk of complications, including recurrent laryngeal nerve injury, hypocalcemia, and bleeding. The American Association of Endocrine Surgeons (AAES) guidelines for managing pHPT (2016) state that experienced parathyroid surgeons have higher success rates and recommend surgical referral for persistent or recurrent hypoparathyroidism to experienced parathyroid surgeons.[1] Instead of focusing on the association between case volume and success rates of parathyroidectomy, this landmark study aimed to evaluate the correlation between surgical volume and the etiology of operative failures.

STUDY DESIGN

This retrospective cohort study utilized data from two prospective endocrine surgery databases from the Medical College of Wisconsin Parathyroid Database (created in 1999) and the University of Wisconsin Parathyroid Database (created in 2001).

SAMPLE SIZE

One hundred and fifty-nine patients with persistent/recurrent hyperparathyroidism who were subsequently cured with additional surgery.

INCLUSION/EXCLUSION CRITERIA

All patients with persistent/recurrent hyperparathyroidism who subsequently underwent curative surgery at either the University of Wisconsin or the Medical College of Wisconsin.

 DOI: 10.1201/9781003196211-35

INTERVENTION OR TREATMENT RECEIVED

The hospital volume of institutions where first-time surgery was undertaken was obtained from a state database of 89 hospitals. High-volume hospitals were defined as those performing >50 parathyroidectomies per year, while low-volume hospitals performed <50 parathyroidectomies per year. Fifty parathyroidectomies represent approximately one parathyroidectomy per week, per institution.

Preventable operative failures were defined as cases where the location of missed abnormal parathyroid glands were accessible through a standard cervical incision, including retroesophageal space, intrathyroidal, and abnormal glands within the thyrothymic ligament. Nonpreventable operative failures were defined as cases where missed abnormal glands were found in a location that was not accessible through a standard cervical incision, including high undescended and deep mediastinal glands. The number of preventable operative failures was compared between high-volume and low-volume hospitals.

RESULTS

Of the 159 study patients, 61 had their initial operations performed in high-volume hospitals and 98 in low-volume hospitals; 84 had a single adenoma missed at the initial operation, whereas 75 had multigland hyperplasia. Despite a higher incidence of multiglandular disease in high-volume hospitals (66% vs. 35%, $p < 0.032$), low-volume hospitals had a higher incidence of persistent hyperparathyroidism ($n = 103$) (87% vs. 43%, $p < 0.0001$). When examining the etiology of initial operative failure, the number of preventable operative failures was significantly higher in the low-volume group than in the high-volume group (89% vs. 13%, $p < 0.0001$). The most common location of missed parathyroid glands in the low-volume group was within the retroesophageal space (57%).

STUDY LIMITATIONS

Limitations of this study include those inherent in data from prospective databases and its retrospective nature. Data were collected from two individual institutions, unavoidably subject to referral bias. The study focused only on patients who had undergone successful reoperative surgery, which biased the outcome. Detailed information, including preoperative workup, operative technique, and use of adjuncts to surgery, such as intraoperative parathyroid hormone monitoring (ioPTH) at initial operations performed outside of the University of Wisconsin and the Medical College of Wisconsin, were not obtained. Given the limitations set by the approved study institutional review board protocol, the identities of the surgeons who performed the initial parathyroid operations were not recorded. Thus, the relationship between surgeon volume and parathyroid surgery outcome could not be evaluated by this study.

STUDY IMPACT

Surgeons have utilized many preoperative parathyroid localization techniques to improve outcomes from parathyroid operations. However, recent data have suggested that these techniques do not improve outcome.[2] Intraoperative adjuncts such as radioguidance,[3]

near-infrared parathyroid autofluorescence,[4,5] and ioPTH[6] may improve outcomes, but ultimately, the success of parathyroid surgery largely depends on the surgeons' experience. Reoperations are associated with a higher risk of complications such as recurrent laryngeal nerve injury, hypocalcemia, and bleeding.[7] Mitigating operative failures from parathyroidectomy, especially avoidable reoperations, would optimize patient outcomes. This retrospective study illustrated that high-volume centers (>50 cases per year) were associated with favorable results from parathyroid surgery, as measured by lower failure rates (less persistent hyperparathyroidism).

This study also demonstrated the importance of surgical experience in performing reoperative parathyroidectomy. The authors defined preventable operative failures as those in which the location of missed abnormal parathyroid glands were accessible through a standard cervical incision and illustrated that low-volume hospitals had significantly more preventable failures than high-volume hospitals. The most common site of missed parathyroid glands in low-volume centers was the retroesophageal space. This finding corroborated the results of a meta-analysis reported by Taterra et al. (2018),[8] who found that 15.9% of parathyroid glands are present in ectopic locations, and 51.7% of the ectopic glands located in the neck are localized to the retroesophageal and paraesophageal spaces.

One of the most critical lessons surgeons can take away from this study is to inspect retroesophageal spaces if they are unable intraoperatively to localize an abnormal parathyroid gland. Since the retroesophageal space is a common location for missed parathyroid glands, surgeons should routinely examine this deep space during the initial parathyroidectomy.

RELEVANT ADDITIONAL STUDIES

The AAES guidelines for managing pHPT (2016) suggest that patients diagnosed with pHPT should be referred to experienced parathyroid surgeons because high-volume surgeons have a higher success rate while minimizing complications, costs, and length of stay.[1] However, the threshold of case volume for high-volume parathyroid surgeons, or medical centers, and the etiology of failure of initial parathyroidectomies in low-volume centers remains unclear.

Subsequent studies have used different thresholds to define low- and high-volume centers. Yeh et al. performed a retrospective study querying the Kaiser Permanente-Southern California Laboratory Management System patient data repository of all members diagnosed with pHPT between 1995 and 2010 who underwent initial parathyroidectomy.[9] High-volume hospitals were defined as ≥100 cases per year, medium volume as 50–99 cases, and low volume as <50 cases. Patients treated at high-volume hospitals (>100 cases) were associated with less operative failure than those treated at low-volume hospitals (odds ratio [OR] 0.42, 95% confidence interval [CI] 0.19–0.92, $p < 0.05$). Abdulla et al. [10] categorized annual hospital volume into five groups (very low [1–4], low [5–9], medium [10–19], high [20–49], and very high [≥50]). Their study found that initial operations at lower-volume hospitals were more likely to require

reoperations (6.5% at very low-volume hospitals vs. 0.14% at very high-volume hospitals, $p < 0.001$). This group showed that reoperation rate (y) could be predicted from the hospital case volume (x), using an almost perfectly fitted hyperbolic function: y = |100/x|.

Donatini et al. performed a nationwide retrospective cohort study in France.[11] Using the Chi-Squared Automatic Interaction Detector method (CHAID), they identified 31 parathyroidectomies per year, per center as the threshold for distinguishing between low-volume and high-volume hospitals. Low-volume centers (<31 cases) were associated with a higher risk of reoperation for pHPT (hazard ratio [HR] 1.597, 95% CI 1.240–2.056, $p < 0.001$). Despite using different thresholds to define high-volume centers, all studies[9–11] have consistently shown high-volume hospitals are associated with better outcomes from parathyroid surgery.

In addition to hospital parathyroidectomy volume, individual surgeon operative volume has also been shown to have an important influence on patient outcome. Neychev et al.[12] compared the surgical outcome of cases performed by four parathyroid surgeons in a community-based teaching hospital with one endocrine surgeon's outcome from a high-volume academic center. They found a comparable cure rate (97% vs. 99%, $p < 0.18$) and complication rate (1% vs. 1%, $p < 0.93$) between the two groups. Meltzer et al.[13] found that high-volume surgeons (≥40 cases per year) had a lower rate of vocal cord paralysis (absolute difference, –1.4%; 95% CI, –2.5% to –0.4%) and performed more outpatient procedures (absolute difference, 25.5%; 95% CI, 19.6–31.0%) when compared to low-volume surgeons (≤20 cases per year).[14]

The realization that parathyroid surgery performed in high-volume centers is associated with better surgical outcomes is essential for both patients and referring physicians when pursuing surgical management of parathyroid disease. Patients with increased medical complexity (age >70 years, obesity, equivocal preoperative imaging, multiple reoperations) should be referred to high-volume centers.[15] Currently, almost half of parathyroidectomies (47.1%) are performed by low-volume surgeons. Al-Qurayshi et al.[16] found that men, Hispanics, and those with Medicaid/Medicare health coverage were more likely to be managed by low-volume surgeons.[17] This could either be due to a lack of awareness of how case volume impacts parathyroid surgical outcomes or limited access to surgical care at high-volume centers. The societies of endocrine surgery and head and neck surgery should continue to promote endocrine surgery as a distinct subspecialty while emphasizing the role of training and better access to high-quality, equitable care for patients with primary hyperparathyroidism.

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CHAPTER 36

Bilateral Operation

Reviewed by Ioan Titus Cvasciuc and Fiona C. Eatock

Landmark Paper

BILATERAL NECK EXPLORATION FOR SPORADIC PRIMARY HYPERPARATHYROIDISM: USE PATTERNS IN 5,597 PATIENTS UNDERGOING PARATHYROIDECTOMY IN THE COLLABORATIVE ENDOCRINE SURGERY QUALITY IMPROVEMENT PROGRAM

Kiernan CM, Wang T, Perrier ND, Grubbs EG, Solórzano CC. *J Am Coll Surg.* 2019;228(4): 652–659. doi: 10.1016/j.jamcollsurg.2018.12.034

RESEARCH QUESTIONS/OBJECTIVES

Bilateral neck exploration (BNE) for the treatment of primary hyperparathyroidism (pHPT) is frequently viewed as the gold standard, yet a majority of surgeons preferentially undertake focused parathyroidectomy, and so there is debate regarding the role that each of these procedures should play in the management of patients with this disease. Availability of accurate preoperative localization imaging has made focused, or unilateral, neck exploration (FNE) feasible. Surgeons, seeking to reduce the rate of complications from parathyroid surgery, have embraced these techniques. Some groups, however, have questioned the equivalence in cure rates of the focused and bilateral operations.[1] This landmark paper examines the outcome from parathyroid surgery for patients whose surgeons submit data to the Collaborative Endocrine Surgery Quality Improvement Program (CESQIP). The primary aims of the study were to compare the respective perioperative outcomes of three groups of patients (BNE, FNE, and FNE converted to BNE) undergoing first-time parathyroidectomy for pHPT.

STUDY DESIGN

Retrospective cohort study in which data were collected from the CESQIP on patients with pHPT from 2014 to 2017.

SAMPLE SIZE

A total of 7,347 patients underwent parathyroidectomy over the 42 months of the study. After exclusions, 5,597 records were analyzed.

DOI: 10.1201/9781003196211-36

INCLUSION/EXCLUSION CRITERIA

Records of patients undergoing first-time parathyroid surgery for pHPT were included. Patients were excluded if under the age of 18 years or undergoing surgery for secondary or tertiary hyperparathyroidism (HPT). Familial or lithium-induced hyperparathyroidism cases and parathyroid cancer cases were also excluded.

INTERVENTION OR TREATMENT RECEIVED

Patients identified from the database were divided into three cohorts depending on the operative approach: BNE, FNE, or FNE converted to BNE. Demographics, preoperative localization imaging, and intraoperative variables, including the use of the intraoperative parathyroid hormone assay (ioPTH), were compared. Postoperative outcomes, including biochemical cure rates, postoperative complications, length of hospital stay, and readmission rates, were also compared. A secondary analysis of outcomes was performed in cases for surgeons undertaking >50% of their cases as FNE and BNE, respectively, and who also each undertook more than 50 parathyroid operations annually.

RESULTS

Eighty-seven surgeons submitted cases to the database, with 23 being considered high-volume surgeons (50 or more cases per year). Sixty percent of cases underwent a focused exploration. The study found that those individuals undergoing BNE were slightly older (63 years vs. 61 years) and more likely to be white. A BNE was undertaken in 40% of cases, and in 15% of cases FNE was converted to a bilateral approach at the discretion of the operating surgeon. Although the majority of patients underwent localization imaging preoperatively (96%), this was slightly more frequent in the planned FNE group (97%) underwent localisation scans of which 97% were positive, compared with the planned BNE group (94%).

Across the entire study, 71% had at least two localization scans. Intraoperative PTH was used in more than 90% of cases regardless of the operative approach; however, 57% of patients undergoing bilateral parathyroid exploration had excision of two or more glands despite 72% having positive localization scans. Of those cases which were converted to BNE, 66% had at least two glands excised, while 95% of FNE cases had a single gland removed.

The rate of postoperative hypocalcemia was similar across the groups, but total complications were more frequent in the BNE and converted-to-BNE groups, though no single complication accounted for that difference. The rate of recurrent laryngeal nerve injury was low in all groups, with no statistically significant difference in incidence across the groups. Surgeon confidence of cure was lower in the BNE group, which may be explained by a smaller proportion of patients in the BNE and converted-to-BNE groups showing a >50% drop in ioPTH by the end of their operation (99% FNE; 95% BNE; 93% converted to BNE). The length of hospital stay was longer following BNE and converted-to-BNE exploration groups and day case surgery less frequent in those groups (51% and 54%, respectively, compared with 75% in FNE).

Although 74% of surgeons submitting data were considered low-volume surgeons (fewer than 50 cases per annum), these surgeons accounted for only 27% of the cases. Four high-volume and five low-volume surgeons undertook BNE in more than 50% of their cases, with two of the high-volume surgeons preferring BNE in greater than 97% of their cases.

STUDY LIMITATIONS

This study is a retrospective analysis of data entered into the CESQIP database by individual surgeons, and although it reports on a large cohort of patients, it reflects the practice of only those surgeons who submit data. It is an initiative of the American Association of Endocrine Surgeons, which relies on data entry by individual surgeons on their own cases. As with all such databases, missing outcome data can be problematic, and analysis can only be undertaken on data collected. These issues may result in bias from incomplete reporting of complications and outcomes, thus preventing meaningful conclusions from being made, particularly for longer follow-up data. Eighty-seven surgeons submitted data, a relatively small number for a country the size of the United States; thus suggesting that a minority of the total cases performed across the country were collected, making it uncertain whether these results are applicable nationally or internationally. In addition, data collected regarding the success of surgery may have been influenced when the surgeon reported "concern for failure" and whether a >50% drop in ioPTH was achieved by the end of surgery, rather than the normalization of calcium and parathyroid hormone levels, meaning the true cure rate in each group remains unknown.

STUDY IMPACT

This study brings together data on a large cohort of patients undergoing parathyroid exploration and gives an insight into the utilization of bilateral and unilateral neck exploration. Despite 96% of patients undergoing preoperative localization imaging, 40% of patients had a planned bilateral approach, which was associated with a significantly higher overall complication rate, and there is some evidence to suggest BNE may be associated with a higher long-term rate of cure.[1] FNE was associated with a 15% conversion rate, higher, even, than the overall rate of multiple gland disease expected in the entire cohort, despite 97% positive localization in the FNE group.

This study also found significant differences in practice across the participating surgeons, with rates of FNE varying from 1% of cases to greater than 50%. When operations from high-volume surgeons, almost exclusively undertaking BNE, were excluded, the outcomes were similar across the whole cohort, with more frequent complications in the BNE group. This article justifies the practice of using FNE to reduce the risk of complications but also highlights the need for adequate training and maintenance of skills in BNE, given the need for conversion in 15% of FNE cases and the rate of failure of localization studies, necessitating planned bilateral exploration.

RELEVANT ADDITIONAL STUDIES

This study showed that 40% of cases underwent planned BNE, and 15% of FNE were converted to BNE, despite a very high usage of localization imaging. Significantly more

complications were reported in the group undergoing BNE, an observation previously reported in a systematic review by Ahmadieh and colleagues[2] comparing BNE with minimally invasive parathyroidectomy (MIP) guided by ioPTH and preoperative imaging, and another by Jinih et al.[3] comparing focused and bilateral approaches.

This article reported a retrospective analysis of surgeon-reported data from the CESQIP database. A similar interrogation of the Eurocrine® database, by Bergenfeltz et al. in 2021[4] showed a lower rate of conversion (8.5%) from focused to bilateral exploration. That study also showed a higher cure rate when two or three localization studies were performed or ioPTH was used. Ishii and co-workers[5] reported on 21,738 adult first-time parathyroid explorations from the UK Registry of Endocrine and Thyroid Surgery (UKRETS), and like the current study, found an increased complication rate with BNE, though particularly relating to postoperative hypocalcemia, which in our selected landmark paper was similar across groups. Interestingly, a study by Hughes et al.[6] showed a conversion rate from FNE to BNE of 19%, slightly higher than reported by Kiernan et al., suggesting this is a common occurrence, though the reasons are unclear.

Norman and colleagues[1] reported on their experience of 15,000 parathyroid operations and after having initially adopted FNE, have returned to BNE due to its higher cure rates. Complication rates were not reported in their study, but operative time and postoperative hospital stay were found to be similar for the two groups.

In 2014, Mekel and co-workers[7] compared outcomes in patients younger and older than 65 years undergoing BNE and FNE and found a higher incidence of multiple gland disease in the older age group, advising a low threshold for proceeding with planned BNE in those older than 65 years.

This reviewed landmark paper by Kiernan et al. provides a context for a balance between FNE and planned BNE, showing that FNE is associated with fewer complications but highlighting that BNE remains important in ensuring successful surgery (as measured by surrogate markers of biochemical cure), especially in patients with multigland disease. Further work investigating long-term rates of complications and true biochemical cure would be useful in defining the best operative approach for treatment of pHPT.

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Chapter 37

Focused Operation

Review by Bianka Saravana-Bawan and Adrienne Melck

Landmark Paper

NO NEED TO ABANDON FOCUSED PARATHYROIDECTOMY: A MULTICENTER STUDY OF LONG-TERM OUTCOME AFTER SURGERY FOR PRIMARY HYPERPARATHYROIDISM

Norlén O, Wang KC, Tay YK, Johnson WR, Grodski S, Yeung M, Serpell J, Sidhu S, Sywak M, Delbridge L. *Ann Surg.* 2015;261(5):991–996. doi: 10.1097/SLA.0000000000000715. PMID: 25565223

RESEARCH QUESTION/OBJECTIVES

Definitive treatment of primary hyperparathyroidism (PHPT) has long been defined by a traditional approach, composed of an open bilateral cervical exploration and visualization of all four parathyroid glands (OPTX), with subsequent excision of the visually identified enlarged glands. The majority of primary PHPT cases, however, are caused by a single parathyroid adenoma rather than multigland disease.[1]

Imaging studies are utilized preoperatively to identify parathyroid adenomas and aid in classifying the etiology of a patient's PHPT as single or multigland disease. Imaging studies that are commonly utilized include ultrasound and sestamibi scans, with further studies such as computed tomography (CT), four-dimensional CT (4DCT), magnetic resonance imaging (MRI), and venous sampling traditionally being reserved for more complex or reoperative cases.[2]

Preoperative localization and identification of single-gland disease allows for unilateral exploration of the target parathyroid adenoma and can be performed through a limited incision by focused parathyroidectomy (FPTX). This not only improves cosmesis and decreases postoperative pain with comparable surgical outcomes to traditional OPTX but has the added benefit of decreased operative time, length of hospital stay, and complications.[3]

Some debate exists regarding the use of imaging alone versus the need for imaging and utilization of intraoperative parathyroid hormone (IOPTH) with FPTX. Proponents of IOPTH cite a decreased incidence of persistent PHPT due to missed disease.[4] In contrast, opponents of IOPTH cite false-negative results, necessitating unnecessary exploration, and false-positive IOPTH resulting in persistent disease and increased operative time, negating much of the benefits of the intended FPTX.[5,6] Siperstein et al. showed that with

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use of IOPTH, up to 16% of multiglandular parathyroid disease cases were missed.[7] Additional studies also suggest lower rates of cure and increased recurrence rates for PHPT after FPTX in comparison to OPTX.[8,9]

This landmark paper was designed to assess and compare rates of persistence, recurrence, and complications in patients undergoing parathyroidectomy by OPTX or FPTX and is the largest reported to date to do so.

STUDY DESIGN

A retrospective multicenter cohort study was performed with data from 1990 to 2013 at two tertiary-care academic hospitals: University of Sydney Endocrine Surgical Unit and the Monash University Endocrine Surgery Unit.

SAMPLE SIZE

A total of 4,569 patients who underwent parathyroidectomy by endocrine surgeons for PHPT, both by OPTX and FPTX without IOPTH, and met inclusion criteria made up the study cohort.

INCLUSION/EXCLUSION CRITERIA

All patients who underwent parathyroidectomy for PHPT (defined as an elevated calcium level with nonsuppressed parathyroid hormone [PTH] or a normal-high calcium level with a high PTH) were included. Patients who had evidence of secondary hyperparathyroidism (HPT), lithium-induced disease, family history of HPT, multiple endocrine neoplasia, familial hypocalciuric hypercalcemia, hyperparathyroidism–jaw tumor syndrome, parathyroid cancer, previous parathyroidectomy at another center, or thoracic surgery alone were excluded.

INTERVENTION OR TREATMENT RECEIVED

From 1990 to 2013 at the University of Sydney and from 1993 to 2013 at Monash University, all patients undergoing parathyroidectomy for PHPT at the respective endocrine surgery units had their cases reviewed.

Data regarding demographic information, preoperative calcium levels, preoperative PTH levels, number and weight of glands resected, and any concomitant thyroid resection were documented. As PTH analysis methods did vary over the duration of the study, all values were adjusted to the most recent lab set range to allow for comparability.

Patients were divided into two cohorts based upon procedure performed, FPTX and OPTX. All patients underwent preoperative and postoperative laryngoscopy.

Cohort 1 was determined suitable for FPTX by positive concordant preoperative functional and anatomical imaging that consisted of a sestamibi scan and ultrasound

or 4DCT. The operative procedure of FPTX was carried out through a 2- to 3-cm incision with location (medial or lateral) based on surgeon preference. The approach was directed to identify and remove the enlarged gland identified by imaging. Conversion to a four-gland exploration was only made if the adenoma could not be identified or the ipsilateral parathyroid was noted not to be enlarged. IOPTH was not routinely used. Postoperatively at 1–2 hours and on day 1 PTH was measured to confirm cure prior to hospital discharge.

Cohort 2 consisted of patients who underwent OPTX due to equivocal imaging, nonlocalizing imaging, or the existence of thyroid pathology requiring resection. The OPTX surgical approach consisted of bilateral neck exploration and visualization of four parathyroid glands. If no pathology or insufficient pathology was identified, common ectopic sites were also explored. PTH was not routinely assessed if patients were noted to be normocalcemic at follow-up.

Postoperatively, routine follow-up for patients treated by both FPTX and OPTX was similar. This included a clinical assessment at 2 weeks and further biochemical assessment of serum calcium levels at 3–12 months. Persistent and recurrent disease, defined by calcium above the upper normal limit of corrected calcium within or after 6 months, respectively, was documented in prospective surgical databases maintained by each institution. In normocalcemic HPT patients, persistent or recurrent disease was defined by a PTH value above normal.

The primary outcome of interest was the difference in proportion of disease persistence between the two cohorts. All patients were analyzed by both an intention to treat (ITT) and by a treatment received (TR) analysis. Persistence rates were also compared temporally before and after widespread introduction of FPTX at the study institutions. The secondary outcomes assessed were differences in cumulative recurrence rates and complications including 30-day mortality, hypoparathyroidism, recurrent laryngeal nerve (RLN) palsy, surgical site infection, and hemorrhage requiring return to the operating room. Hypoparathyroidism was defined as symptomatic disease requiring additional calcium or vitamin D treatment. Permanent RLN injury and hypoparathyroidism were defined as persistence past 6 months postprocedure. Analysis was with X^2, with sample size determined using a power of 80%, and α level of 0.05 was planned. The sample size calculation required a minimum of 1,533 patients per cohort to demonstrate a difference between persistence and recurrence rates of 3.0% and 1.5%, respectively.

RESULTS

A total of 4,569 patients met study inclusion criteria and were included for assessment. The median duration of follow-up was 6.5 years (range 1.0–24.0 years). Of the 4,569 patients, 2,531 were treated with ITT-FPTX, 164 cases required conversion, and, as such, 2,367 patients received FPTX, while 2,038 patients underwent ITT-OPTX.

Between the two patient cohorts, demographic variables were similar. The mean calcium level, PTH level, and weight of resected glands were higher within the

ITT-FPTX group. As anticipated, the ITT-FPTX had a lower mean number of parathyroid glands resected and a lower rate of concomitant thyroid surgery. The indication for thyroid surgery was benign nodular disease in 83% of patients and thyroid cancer in 9% of patients. Serum calcium levels were available for 99% of patients within a year postprocedure for assessment. A total of 103 and 40 patients had persistent and recurrent disease, respectively. Primary outcome analysis by both ITT and TR revealed a statistically significant increased rate of persistence in the FPTX group as compared to the OPTX group (2.7% vs. 1.7%, $p = 0.036$ and 2.7% vs. 1.8%, $p = 0.043$ respectively). There was a trend toward a higher long-term recurrence rate in the ITT-FPTX compared to the ITT-OPTX group at 10 years (1.8% vs. 0.9%); however, this did not reach statistical significance, and the trend was not present at 5 years of follow-up.

Another secondary analysis was performed for the 3,070 patients who underwent PTX alone without a concomitant thyroid procedure. Within this group, 920 patients underwent ITT-OPTX and 2,050 underwent ITT-FPTX with no statistical difference in either persistence rates (2.2% vs. 2.3%, $p = 0.895$) or 5-year recurrence rates between the two groups (0.7% vs. 0.8%, log-rank $p = 0.144$).

For analysis of complications, patients with concomitant thyroid resection were excluded. There were no 30-day mortalities associated with surgery or as a consequence of surgery. RLN palsy between the ITT-FPTX and ITT-OPTX cohorts was not statistically different whether temporary (1.2% vs. 0.8%, $p = 0.361$) or permanent (0.3% vs. 0.4%, $p = 0.893$). A single patient in the ITT-OPTX group did require prolonged intubation and temporary tracheostomy for bilateral RLN palsy.

Rates of temporary hypoparathyroidism were statistically lower in the ITT-FPTX compared to ITT-OPTX cohort (0.8% vs. 2.9%, $p < 0.001$), but there was no difference in rates of permanent hypoparathyroidism. Overall, complications were more frequent in the ITT-OPTX group compared to the ITT-FPTX group (7.6% vs. 3.6%, $p < 0.001$) with both the incidence of hemorrhage (1.5% vs. 0.4%, $p = 0.001$) and wound infection (0.8% vs. 0.2%, $p = 0.021$) being higher.

One hundred and eighteen of the 143 patients with either persistent or recurrent disease underwent reoperation. Pathology revealed 22 cases of hyperplasia, 22 cases of a single adenoma which was not identified at initial procedure, 38 cases of a contralateral double adenomata, two cases of mediastinal double adenomata, and three cases of double adenomata with no note of laterality.

STUDY LIMITATIONS

The main limitations of this study are due to its retrospective nature. Patients could not be randomized to procedure, raising the question of selection bias. Moreover, there is little documentation within the article as to how selection for planned FPTX over OPTX was made apart from surgeon choice. This could have led to significant selection bias in the choice of the patient procedures.

Patients were followed by the surgical center for 12 months with subsequent follow-up performed in the community, and longer-term follow-up was not ascertained on review. As such, although the median follow-up was 6.5 years, the range indicates that some patients were followed up to the minimum of 1 year, and accordingly, cases of recurrent disease may have been lost to follow-up and therefore underestimated in this study.

The group did perform a power-based sample size calculation and determined that a total of 1,533 patients would be required in each cohort. However, as a result, and potentially to meet the required study numbers, a lengthy time interval was utilized for the study period, from 1990 to 2013. With such a long timeframe, it is likely that the imaging modalities and surgical approaches would have changed, resulting in bias if timeframes were not balanced between the two surgical cohorts or affected one cohort differentially.

Furthermore, the article notes that the main onset of FPTX at the surgical centers was in 1998, which could introduce bias, as the rates of complications and conversion, in addition to more selective patient selection for FPTX, could have varied as surgeons were first introducing FPTX into their practices. Although the study did perform an analysis to assess if persistence rates differed before and after January 1998, this was not stratified by operation type, and changes due to more widespread performance of FPTX could therefore have been dampened by OPTX cases. Additionally, as 1998 was noted to be the year when FPTX became increasingly utilized, analysis to assess the potential existence of "growing pains" with the introduction of the procedure should likely have been performed at a later point.

Lastly, one must consider the potential impact of surgeon volume and experience as a potential confounder. Although all procedures were performed by endocrine surgeons in an endocrine surgery unit at either the University of Sydney or Monash University, there is no breakdown or analysis of procedures and outcomes based on surgeon experience. This does also highlight a salient point with regard to the generalizability of this study in that it demonstrates the comparability of outcomes by FPTX and OPTX when performed by endocrine surgeons and that outcomes may differ if performed by surgeons with less experience or training in parathyroid assessment and surgical procedures.

STUDY IMPACT

Minimally invasive operative approaches for the treatment of PHPT have become increasingly widespread over the past decade, with surgeons citing improved patient satisfaction, cosmesis, and quality of life, as well as decreased operative times, analgesia requirements, and costs.[10–12] However, as proponents of this approach explored more focused approaches, with the utilization of radioguidance, video guidance, or even endoscopic parathyroidectomy, the publication of studies reporting on conflicting outcomes began to raise questions regarding the role of FPTX. Institutions began exploring results of FPTX and OPTX, with multiple retrospective analyses identifying increased recurrence rates after FPTX compared to OPTX.[9,13,14]

Accordingly, this landmark paper was a response to evaluate outcomes of FPTX in comparison to OPTX in high-volume FPTX centers. This multi-institutional robust analysis demonstrates the benefit of FPTX with comparable long-term recurrence rates (0.6% vs. 0.4%) but significantly improved overall complications with FPTX compared to OPTX (3.6% vs. 7.6%, $p < 0.001$).[3] Additionally, although this study did demonstrate statistically significant differences in persistence rates with FPTX compared to OPTX (2.7% vs. 1.7%, $p = 0.036$), this difference would only result in 1/100 patients who'd undergone FPTX requiring reoperation. This is emphasized by the observation that patients undergoing subsequent reoperation for persistent disease were all cured at reoperation and had no increased risk of complications.[3]

RELEVANT ADDITIONAL STUDIES

A systematic review and meta-analysis by Jinih et al. assessed the outcomes of FPTX in comparison to OPTX for PHPT treatment. This systematic review identified 19 studies with a total of 12,743 patients. Primary outcomes of disease recurrence (odds ratio [OR] 1.08, 95% confidence interval [CI] 0.59–2.00, $p = 0.80$) and persistence (OR 0.89, 95% CI 0.58–1.35, $p = 0.58$) were comparable between the two operative groups. Secondary outcomes of complications (OR 0.35, 95% CI 0.15–0.84, $p = 0.02$) and operative time (mean difference –39.86, 95% CI –53.05 to –26.84, $p < 0.01$) were decreased in the FPTX group. Within this study, the recurrence rate in the FPTX group was 1.25% compared to 0.8% in the OPTX group, and while not statistically significant, this variance was believed to be impacted by the inclusion of studies not utilizing IOPTH in the FPTX cohort.[14]

A Cochrane review of FPTX with IOPTH compared to OPTX for treatment of PHPT only identified five eligible studies with a total of 266 patients. This study demonstrated a success risk ratio for FPTX compared to OPTX of 0.98 (95% CI 0.94–1.03, $p = 0.43$), demonstrating no difference in outcomes between these surgical approaches. Long-term outcomes could not be reliably assessed, as only one study included these. This meta-analysis did not demonstrate superiority of one operative approach over the other, although studies were noted to overall be of low-certainty evidence.[15] Quinn et al. published a systematic review and meta-analysis comparing FPTX with IOPTH and FPTX performed without IOPTX. A total of 12 studies with 2,290 patients were identified for inclusion. This meta-analysis demonstrated that although patients treated with FPTX had a higher rate of conversion to bilateral exploration (OR 3.55, 95% CI 1.27–9.92, $p = 0.02$), the utilization of IOPTH led to an improved cure rate (OR 3.88, 95% CI 2.12–7.10, $p < 0.001$).[16] This supports the use of IOPTH in FPTX enabling similar cure rates to OPTX but with fewer complications.

In conclusion, the literature is concordant with the findings of the landmark paper reported by Norlén et al. With regard to surgical outcomes, FPTX and OPTX are comparable in terms of their cure rates, but FPTX is associated with fewer postoperative complications and should be considered as the preferred surgical approach in patients with localizable disease.

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Chapter 38

Intraoperative PTH Measurement

Review by Hiba Fatayer and Susannah L. Shore

Landmark Paper

COMPARISON OF INTRAOPERATIVE iPTH ASSAY (QPTH) CRITERIA IN GUIDING PARATHYROIDECTOMY: WHICH CRITERION IS THE MOST ACCURATE?

Carneiro DM, Solorzano CC, Nader MC, Ramirez M, Irvin III GL. *Surgery.* 2003;134(6): 973–979. doi: 10.1016/j.surg.2003.06.001

RESEARCH QUESTION/OBJECTIVES

The use of intraoperative quick parathyroid hormone assays (QPTHs) has evolved over the past 20 years and gained significant popularity in its use as an intraoperative adjunct during parathyroidectomy. These assays measure changes in circulating hormone levels. This helps in confirming intraoperative cure and leads to successful outcomes, with a reduction in bilateral neck explorations and potentially shorter operative times. They can also help to localize hypersecreting parathyroid glands when used in conjunction with intraoperative internal jugular vein sampling. The utilization of intraoperative QPTH is still widely debated in first-time surgery for primary hyperparathyroidism, with protagonists and antagonists throughout the world of endocrine surgery.[1–4] The case for intraoperative QPTH has been difficult to categorically prove due to the differences in protocols and methods of analyzing PTH. Variation in sample timings according to the criteria requirements to predict intraoperative success has accounted for these differences.

This landmark paper compares the outcomes from limited parathyroidectomy for sporadic primary hyperparathyroidism using the Miami criteria versus five other different QPTH protocols that are employed around the world. The Miami criteria[5–8] state that a ≥ 50% drop of intact parathyroid hormone (iPTH) from the highest (pre-incision or pre-excision) level to 10 minutes after excision of all abnormal parathyroid gland(s) is accurate in predicting postoperative normalization of calcium levels. This guides the surgeon to terminate the procedure without further exploration or visualization of the other parathyroid glands.

The primary aim of this landmark paper was to report on the different degrees of accuracy of the Miami criteria versus other published protocols when applied to a large cohort of patients, with sporadic primary hyperparathyroidism with a high calcium

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and parathyroid hormone, who underwent parathyroidectomy guided by intraoperative parathyroid hormone (PTH) measurement.

STUDY DESIGN

A retrospective analysis of a cohort of consecutive patients with sporadic primary hyperparathyroidism (SPHPT) who underwent limited parathyroidectomy using the Miami criteria to confirm cure prospectively. All study patients had undergone a technetium 99m sestamibi scan, and some cervical ultrasonography preoperatively. Patients who were followed ≥6 months or were recognized as operative failures were included.

Blood sampling of 4 mL peripheral venous or arterial blood was obtained in all patients at four specific time points: pre-incision, pre-excision (after dissection and just before clamping the suspected gland's blood supply), 5 minutes, and 10 minutes after single or multiple gland resections (time 0 is when clamping the gland's blood supply).

If iPTH failed to drop sufficiently according to the Miami criteria, this would prompt the surgeon to continue exploring the neck, and when further parathyroid tissue was excised, then blood was drawn for iPTH measurement and the QPTH test repeated. The outcomes of surgery of five other QPTH criteria, described later, were then retrospectively calculated and compared to the outcome using the Miami criterion.

Intraoperative iPTH levels were retrospectively reanalyzed with the use of five published criteria to predict cure:

1. A ≥50% iPTH drop from pre-incision level only 10 minutes after parathyroid gland excision[9–15]
2. A ≥50% iPTH drop from the highest (pre-incision or pre-excision) levels 10 minutes after excision of all abnormal parathyroid gland(s) with iPTH returning to normal range[9,16,17]
3. A ≥50% iPTH drop from the highest (pre-incision or pre-excision) levels 10 minutes after excision and falling below the pre-incision iPTH level[18]
4. A ≥50% iPTH drop from the highest (pre-incision or pre-excision) levels 5 minutes after excision[6,19]
5. A ≥50% iPTH drop from the pre-excision level only 10 minutes after gland excision[13]

SAMPLE SIZE

Three hundred and forty-one patients (308 initial operations and 33 reoperations) who underwent limited parathyroidectomy made up the study population.

INCLUSION/EXCLUSION CRITERIA

SPHPT patients who underwent limited parathyroidectomy and were followed ≥6 months were included in this study population. Cases with negative or equivocal

localization studies were included if intraoperative differential jugular venous sampling was used to help guide the surgery. Published criteria that included patients who had blood sampling later than 10 minutes were excluded, as samples in this series were rarely collected after 10 minutes following gland excision.

INTERVENTION OR TREATMENT RECEIVED

Day 1 postoperative serum calcium levels were taken, and serum calcium and iPTH were measured at 2 and 6 months postoperatively, and then yearly to correlate with criteria predictions. Data from 341 patients was used to evaluate criteria 1, 3, 4, and 5, and data from 255 patients was used to evaluate criteria 2 because one of the assays used had no published normal range for iPTH in 86 patients.

The sensitivity (TP / TP + FN), specificity (TN / TN + FP), positive predictive value (TP / TP + FP), negative predictive value (TN / TN + FN), and accuracy (TP + TN / TP + TN + FP + FN) of each criteria was calculated. True positive (TP) was defined as the correct prediction of normocalcemia at 6 months postoperatively, true negative (TN) the correct prediction of incomplete excision, false positive (FP) as the incorrect prediction of normocalcemia (i.e., patient remained hypercalcemic postoperatively), and false negative (FN) as the incorrect prediction of postoperative hypercalcemia, which might have prompted unnecessary bilateral neck exploration and/or prolonged operative time.

RESULTS

Operative success was achieved in 331 of 341 (97%) cases using the Miami criteria, and patients with multiglandular disease were identified in 4%. Postoperative calcium levels were correctly predicted for 329 of 341 (96%) patients. Among the 329 patients who had correctly predicted operative outcomes, 322 (89.7%) were TP and remained normocalcemic 6 months postoperatively. Whereas 69 (21%) were TN, 7 were known operative failures and the remaining 62, guided by an insufficient drop in iPTH, underwent further exploration during the same procedure and complete resection of the abnormal gland(s). All except a single patient remained normocalcemic postoperatively. On the other hand, the operative outcomes were incorrectly predicted in 12 of 341 (3.5%) patients, three had FP and nine had FN results.

In the three FP cases, one patient developed hypercalcemia recurrence despite an 82% iPTH drop from the pre-incision level at 10 minutes after single-gland excision (at re-excision, parathyroid cancer was diagnosed), one was due to technical assay error in analyzing the iPTH in the sample, and the third was influenced by parathyroid cyst rupture leading to a surge in the iPTH pre-excision level. In the nine FN cases, continued exploration in two cases failed to localize additional abnormal gland(s), and the remaining seven cases did not undergo further exploration, as iPTH dropped significantly at 20 minutes. All nine FN patients were normocalcemic postoperatively.

When compared to the Miami criteria, each of the other five published criteria would have avoided one or two FP outcomes, but at the expense of an increase in the FN

cases from 2.6% to 6–24%, potentially resulting in more unnecessary bilateral neck explorations ($p < 0.05$). In other words, application of these stricter alternative criteria predicted an increase in specificity of QPTH at the expense of its sensitivity and reduced the overall accuracy of QPTH compared to the Miami criteria.

With the utilization of the Miami criteria but measuring iPTH drop at 5 minutes post-excision rather than 10 minutes would have resulted in 30/322 (9%) of TP cases not demonstrating a >50% drop of iPTH. Using an alternative criterion to the Miami criteria resulted in a reduction of two out of three FTP, but at the risk of increasing the FN incidence from 2.6% to 6–24%.

STUDY LIMITATIONS

The main limitation of this study was its retrospective analysis. Details on data collection, assays used, duration of the study period, total length of follow-up, and recurrence rates were not clearly identified. The study excluded protocols that involved checking iPTH beyond 10 minutes, since most of their studied cases seldom required blood tests later than 10 minutes. It would have been valuable to include these protocols and see if they differ in outcome, especially given that 77.8% (seven out of nine) of the FN cases did not have further cervical exploration, as iPTH dropped significantly at 20 minutes. The study also reported a very low incidence of multigland disease (4%) compared to published data; this may introduce an element of bias into the data.

STUDY IMPACT

The use of intraoperative PTH monitoring was first introduced by Irvin et al. in 1990 after failing to cure a patient with primary hyperparathyroidism (PHPT) following removal of a single parathyroid adenoma at bilateral neck exploration and parathyroidectomy.[5–8] He used a "quick PTH assay," which exploits the short half-life for PTH of 3–5 minutes. Many modifications to the original PTH assay have been made, and in current practice iPTH is commonly measured by rapid immunoassay.[1]

Carniero et al. was the first study to establish the accuracy of the Miami criteria compared to other published criteria in predicting complete excision of abnormal parathyroid gland(s),[20] offering clear guidance on the best protocols to use for consistency of cure, and importantly, for decreasing unnecessary bilateral neck explorations. The criteria demonstrate that ≥ 50% iPTH drop from the highest (pre-incision or pre-excision) level at 10 minutes after gland excision can predict cure at 6 months in up to 97% of cases, comparable to outcomes from bilateral neck exploration.

The implementation of accurate intraoperative PTH monitoring enabled early confirmation of biochemical cure following the excision of abnormal parathyroid gland(s), improved cure rates from limited parathyroidectomy, and shifted the surgical approach from a standard bilateral neck exploration to a more focused and less invasive approach.

The Miami criteria have been evaluated against other commonly applied criteria, including the Halle, Rome, and Vienna criteria, in guiding minimally invasive parathyroidectomy (MIP).[3] The predictive value of the Miami criteria was superior to other criteria, with the highest intraoperative predictive accuracy of cure. Other published criteria have been tailored to adapt the surgeon's needs and cut down cost, resulting in fewer blood samples collected during the operation, but leading to a decrease in the sensitivity of intraoperative PTH in predicting postoperative normocalcaemia.[9–13,15,21]

The Miami criteria have been widely recognized and adopted by many units to help predict biochemical cure following parathyroidectomy for PHPT. This landmark paper helped establish the greater accuracy of the Miami criteria compared to other protocols.

RELEVANT ADDITIONAL STUDIES

The utility of intraoperative PTH as an adjunct to MIP has become widely used by surgical units worldwide. Despite its popularity, controversy remains regarding its need, especially when a pathological parathyroid gland has been localized by concordant dual imaging. Detractors argue that iPTH increases costs and operative time with minimal benefit to a first-time MIP guided by concordant preoperative localization studies.[4,22–25] Barczynski et al. showed that iPTH is most useful in patients with positive but discordant imaging,[22] and Suliburk et al. suggested that routine use of iPTH is not necessary in first-time surgery for PHPT.[25] Shawky et al., on the other hand, demonstrated an added value of 14% in achieving cure ($p < 0.05$) with routine iPTH use, including first-time surgery (11% added value), where added value is the percentage of patients where intraoperative PTH contributed to the cure.[26]

A systematic review and meta-analysis by Quinn et al. evaluated the cure rates following MIP with the use of intraoperative PTH.[27] Out of 12 studies reporting on 2,290 PHPT patients, the use of iPTH was associated with higher cure rates of 98% ($n = 1,032$), compared to cure rates of 94.8% ($n = 1,020$) in those not treated with iPTH ($P < 0.001$). Failure to cure rates were reported by 10 studies, and failure rates were lower in the iPTH group (0.98%; $n = 9$) compared to the group without iPTH (5.65%; $n = 55$) (odds ratio [OR], 0.24; 95% confidence interval [CI] 0.12–0.45; $P < 0.001$). There was a trend toward longer surgery in the iPTH group ($P = 0.06$), and the need for bilateral neck exploration was greater for the iPTH group compared with the non-iPTH group ($P = 0.02$), which likely is due to the presence of multiglandular disease (MGD) or double adenomas. The authors advocate for routine use of iPTH in MIP to facilitate higher cure rates and with no increased morbidity with iPTH use.

The value of iPTH monitoring and cost was addressed by a literature review of 17 studies involving 4,280 patients who underwent MIP.[28] Estimations of base case cost and probabilities using a decision-tree model were used to analyze the cost of iPTH based on preoperative imaging accuracy, reoperation cost, MGD rate, and iPTH cost. This study concluded that intraoperative PTH increased the rates of cure marginally from 96.3% to 98.8% while adding approximately 4–20% additional cost (ranging between 266.24 USD

and 1,000 USD, depending on the required iPTH tests). They considered iPTH use to be cost saving when reoperation costs increase above $12,000. On the other hand, a retrospective cohort study from a single high-volume unit analyzed the impact of iPTH on the decision-making and cost-effectiveness.[29] Out of 114 cases included, a cure rate of 99.1% (113 out of 114) was achieved, and 13/114 (11.4%) of cured cases were influenced by iPTH use (including 7.1% with concordant imaging). The cost-effectiveness of iPTH was demonstrated in this study by comparing the total cost of iPTH use over 2 years with the potential cost of reoperative procedures if iPTH hadn't been undertaken, showing a significant reduction of cost per reoperative procedure avoided.

Finally, the European Society of Endocrine Surgeons (ESES) recommends the use of iPTH with nonconcordant preoperative imaging or a single imaging modality,[30] whereas the American Association of Endocrine Surgeons (AAES) recommends the use of iPTH routinely for focused parathyroidectomy guided by imaging to avoid missing MGD and reduce failure rates.[31] However, the British National Institute for Health and Care Excellence (NICE) guidelines suggest that it should not be used in first-time surgery.[32] This inconsistency in recommendations suggests that controversy regarding the use of iPTH has not yet been resolved. Indeed, some units argue that the pendulum has swung back to performing bilateral neck explorations due to higher recurrence rates with focused parathyroidectomy,[33] while many others continue using iPTH to improve their outcomes.

However, the landmark paper reviewed clearly demonstrated the Miami criteria to be superior to other published criteria for iPTH, and it yields results equivalent to bilateral neck exploration.

DEFINITIONS OF TERMINOLOGY USED

Limited Parathyroidectomy: Defined as parathyroid resection guided by intact parathyroid hormone (iPTH) level dynamics provided by a quick iPTH assay and assisted by preoperative localization studies.

Operative Success: Normal or low calcium for at least 6 months after parathyroidectomy.

Operative Failure: Persistent hypercalcemia and elevated iPTH within 6 months of surgery.

Recurrent Hyperparathyroidism: Hypercalcemia and elevated iPTH ≥6 months following parathyroidectomy.

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CHAPTER 39

Remote Access Operation

Review by Priscilla Francesca Procopio, Francesco Pennestrì, and Marco Raffaelli

Landmark Paper

ONE HUNDRED AND ONE CONSECUTIVE TRANSORAL ENDOSCOPIC PARATHYROIDECTOMIES VIA THE VESTIBULAR APPROACH FOR PHPTH: A WORLDWIDE MULTI-INSTITUTIONAL EXPERIENCE

Grogan RH, Khafif AK, Nidal A, Anuwong A, Shaear M, Razavi CR, Russell JO, Tufano RP. *Surg Endosc*. 2022;36:4821–4827. doi: 10.1007/s00464-021-08826-y

RESEARCH QUESTION/OBJECTIVES

Since the introduction of the vestibular approach to neck surgery, an increasing number of transoral parathyroidectomies has been performed in numerous institutions across the world with growing interest and satisfactory results for this "scarless" surgery.[1,2] Despite the improved local cosmesis, the adoption of these techniques has been slow and met with skepticism due to unfamiliar dissection planes, steep learning curves, longer operative times and novel complications.[1,3] The primary aim of the selected landmark paper was to determine whether transoral endoscopic parathyroidectomy via the transoral vestibular approach (TOEPVA) can be successfully performed in a safe and efficient manner by presenting the largest series of cases to date.

STUDY DESIGN

Prospective study of a series of consecutive TOEPVA cases performed between 2017 and 2020 in multi-institutional, academic, high-volume transoral thyroidectomy centers from the United States, Israel and Thailand.

SAMPLE SIZE

One hundred and one patients who underwent focused transoral parathyroidectomies.

INCLUSION/EXCLUSION CRITERIA

Patients with preoperative diagnosis of primary hyperparathyroidism (PHPTH) and single, well-localized parathyroid adenoma were considered eligible. Indication for surgery was based on established international workshop guidelines for either symptomatic or asymptomatic hyperparathyroidism. Preoperative well localization was defined as two concordant imaging studies, namely a combination of two of any

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of the following: 4D-CT, sestamibi, or ultrasound. PHPTH patients without definitive preoperative localization of a single adenoma were excluded. Patients with secondary or tertiary hyperparathyroidism were not included. Similarly, patients with suspected or confirmed multiple endocrine neoplasia type I (MEN1) were not included due to multiglandular disease.

INTERVENTION OR TREATMENT RECEIVED

Surgical success was defined by normalization of postoperative PTH levels. Conversions to open cervical exploration were described, as well as the intraoperative detection of multigland disease. Postoperative complications included temporary or permanent hypoparathyroidism, recurrent laryngeal nerve injury, wound infection, skin injury and mental nerve injury. Operative time (OT) in the four participating institutions was compared. Learning curve, parathyroid surgery volume, transoral endocrine surgery experience and parathyroid size were considered as predictive variables affecting OT.

RESULTS

The overall surgical success rate of the operations was 98% (99 patients), with two cases not returning to normal PTH levels in the immediate postoperative period. Three conversions to open exploration (3%) have been described, due to nondescending intraoperative parathyroid hormone (IOPTH) levels after the resection of a preoperatively identified parathyroid adenoma. All three cases were found to be caused by multigland disease despite well-localized preoperative imaging. No cases of temporary or permanent hypoparathyroidism and/or permanent recurrent laryngeal nerve injury were reported. One case of temporary recurrent laryngeal nerve palsy (1%) occurred, which spontaneously recovered. One wound infection (1%) and two skin injuries (without further specification) (1.98%) were also reported. The median overall OT for all four institutions combined was 112 minutes (interquartile range [IQR] 97 minutes). The median overall OT for each institution showed a significant difference between the four institutions ($p < 0.001$). The learning curve effect on OT was determined by comparing the OT of the first half of cases to the OT of the second half of cases for each institution. A statistically significant drop in OT between these two intervals was observed (from 130.5 minutes to 66.5 minutes). A multivariable linear regression model was utilized in order to understand the factors that may affect OT. Predictor variables included in the model were sequential case number, percentage of the practice devoted to parathyroid surgery, level of transoral endocrine surgery experience and parathyroid gland size in centimeters. All the considered factors were found to be statistically significant, except for the parathyroid gland size. The amount of transoral experience and the volume of parathyroid surgery in clinical practice were responsible for the majority of the impact on OT. However, when the model was run on the second half of cases, the only statistically significant variable that impacted OT was the volume of parathyroid surgery, while the amount of transoral experience no longer impacted the OT. Finally, these OT regression models showed that a surgeon who has 30% of their practice devoted to parathyroid surgery and progresses

to at least 50 transoral cases per year can expect to routinely perform transoral parathyroidectomies in 60 minutes or less.

STUDY LIMITATIONS

This study presents several limitations. First of all, despite data being prospectively collected, it is not a comparative study, as it does not compare minimally invasive parathyroidectomy (MIP) and TOEPVA results. Therefore, the actual equivalence to the traditional approach cannot be assessed. Only a randomized clinical trial could definitively assess such an end point. Second, the technical expertise in parathyroid surgery was not homogeneous between the centers. Indeed, two of the four institutions had a small percentage of their practices focused on parathyroid surgery. Moreover, three of the four institutions had no expertise in the transoral approach during the first part of data collection. As a consequence, the learning curve affected the results in terms of OT in all the centers. However, the learning curve was not defined with strict statistical methods, as the authors did not provide any definition of the number of patients or months devoted to TOEPVA that were required to achieve an OT decrease. A further study limitation is related to the results in terms of efficacy of the procedure, since definition of cure was based only on PTH levels measured either intraoperatively or within 24 hours following the operation.[4,5] No follow-up data were provided. Moreover, data from this regard were inhomogeneous among the different centers, since not all of the centers adopted the same criteria. Finally, new potential complications specifically related to the procedure were not precisely addressed and discussed (including CO_2 embolism, oral commissure tears, skin flap burn, mental nerve injury, chip flap perforation and oral commissure or inferior labial frenulum tear).[6–8]

STUDY IMPACT

It is due to avoidance of a cervical incision that the vestibular approach to endocrine neck surgery has continued to grow in popularity in recent years. However, while several case series on the endoscopic approach to thyroid surgery have been reported in literature, only a small amount of informations on TOEPVA is available.[9,10] Moreover, other published studies lacked consistency and qualitative evidence. The present landmark paper considered 101 cases of a scarless approach to parathyroidectomy, representing the largest series of TOEPVA to date, in a multicenter prospective study design over a 2-year period. Such a study design demonstrates the feasibility of this novel surgical approach. Furthermore, previously published review articles suggested that the TOEPVA cure rate and risk of complications are comparable to the conventional approach (96% and 3.8%, respectively).[1] The results of the present landmark paper prospectively demonstrate that the outcomes of TOEPVA in terms of cure and complication rates are comparable to those reported for MIP.

RELEVANT ADDITIONAL STUDIES

Bilateral cervical exploration was considered the standard surgical approach for the treatment of PHPTH. The paradigm shifted when unilateral parathyroidectomy was proposed for the treatment of parathyroid adenoma.[4,5,11,12] Thus, surgeons have adapted a variety of methods to streamline parathyroidectomy and reduce the risk of complications, collectively termed MIP. All MIP surgical approaches aim to limit dissection, hasten recovery, reduce postoperative discomfort and reduce incision length.[4,5,13–15] With the purpose of providing the solution to the impact of cervical scar on health-related quality of life, remote-access surgical approaches, such as those carried out through areolar or axillary incisions, have succeeded in avoiding an anterior neck incision by relocating the cutaneous incision to less conspicuous locations.[6,9,10,16–18] Despite the improved local cosmesis, these techniques may be challenging due to unfamiliar dissection planes and novel complications.[1,3,6,17,19,20] Indeed, the extracervical approaches do not actually comply with the use of the term "minimally invasive," because they are associated with an extensive dissection of the chest and neck region. Noteworthy, from a theoretical point of view, access carried out through anatomically defined planes allows the surgeon to avoid opening the cervical muscle layers, especially the platysma muscle. Thus, one of the main advantages for the patients could also be the absence of postoperative non-neurogenic odynophagia or scarring-related disorders even during the direct postoperative course, despite this not yet being demonstrated.[7,21]

Since the introduction of transoral thyroid and parathyroid operations performed through a transoral vestibular approach by Anuwong in 2016, this technique has been performed worldwide, with growing interest for scarless surgery.[1,2] Because of the short distance between the sublingual space and the thyroid and parathyroid glands, transoral access could theoretically allow the surgical dissection with minimal trauma.[21] In 2017 Sasanakietkul proved that TOEPVA is a feasible and safe procedure for the treatment of PHPTH, yielding an excellent cosmetic outcome with no surgical scar.[2] Afterward, several reports outlined the reasonable success and low complication rates of this surgical technique when performed in a very carefully selected patient population and at high-volume centers.[13,22] In an attempt to standardize the transoral endoscopic vestibular approach, in 2018 the leading groups published a suggested framework for assessment and safe exploration of transoral thyroidectomy and parathyroidectomy.[23,24] However, adequate surgical volume, medical and administrative support and a step-wise learning process are necessary to achieve good results.[24–26] Since the major advantage of this approach is the cosmetic result, the implementation of transoral endocrine neck procedures still poses some important ethical and medico-legal considerations.[27,28] Therefore, patients should be adequately counseled before the surgical procedure.[27,28] Moreover, cadaveric simulation should play an important role in helping surgeons attain the required technical skills.[27,28]

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CHAPTER 40

Parathyroid Cryopreservation

Review by Abby Gross and Eren Berber

Landmark Paper

CRYOPRESERVATION OF PARATHYROID TISSUE: AN ILLUSTRATED TECHNIQUE USING THE CLEVELAND CLINIC PROTOCOL

Agarwal A, Waghray A, Gupta S, Sharma R, Milas M. *J Am Coll Surg.* 2013;216(1):e1–e9. doi: 10.1016/j.jamcollsurg.2012.09.021

RESEARCH QUESTIONS/OBJECTIVES

Permanent hypoparathyroidism, generally defined as insufficient parathyroid hormone to maintain normocalcemia with adequate daily intake of calcium and vitamin D longer than 6 months after surgery,[1] is a rare but detrimental complication of thyroid and parathyroid operations. The rate of permanent postsurgical hypoparathyroidism is estimated to be 0.12–4.6%.[1] However, rates of permanent hypoparathyroidism have been reported to be up to 10% after initial surgery for multiglandular hyperplasia and up to 30% of patients requiring reoperation for persistent or recurrent hyperparathyroidism.[2–4] Autotransplantation of the parathyroid gland remains the primary surgical tool for addressing permanent hypoparathyroidism after thyroid or parathyroid surgery. Cryopreservation permits parathyroid tissue storage for delayed autotransplantation without compromising cellular integrity or function. Parathyroid cryopreservation is indicated for initial neck operations that have a high risk for permanent postoperative hypoparathyroidism (subtotal, near-total, or total parathyroidectomy) and reoperative parathyroid procedures for persistent or recurrent hyperparathyroidism, given their increased risk of permanent hypoparathyroidism.[5] Despite clinical indications for parathyroid cryopreservation, this resource is available to <30% of endocrine surgeons in the United States.[5] This landmark paper describes a successful institutional technique for cryopreservation, specimen storage, and autologous transplant over a 10-year period to facilitate efforts by surgeons to establish cryopreservation for autologous parathyroid transplantation in order to improve patient postoperative outcomes.

STUDY DESIGN

This was a single-institution retrospective cohort study conducted between 2002 and 2012 evaluating the success of autotransplantation of cryopreserved parathyroid glands.

DOI: 10.1201/9781003196211-40

SAMPLE SIZE

Over the 10-year study period, there were over 2,000 parathyroid operations performed at the Cleveland Clinic. From these operations, 630 specimens were cryopreserved, and 9 of those cryopreserved specimens were eventually autotransplanted.

INCLUSION/EXCLUSION CRITERIA

All adult patients undergoing parathyroidectomy at the Cleveland Clinic (Cleveland, Ohio) between 2002 and 2012 were included in the retrospective study. Indications for parathyroid cryopreservation were initial neck operations with a high risk for permanent postoperative hypoparathyroidism (subtotal, near-total, or total parathyroidectomy) and reoperative neck procedures. Parathyroid autotransplantation was performed for symptomatic permanent hypoparathyroidism.

INTERVENTION OR TREATMENT RECEIVED

Cryopreservation

Parathyroid operations with a high likelihood of requiring cryopreservation are scheduled early in the day to ensure adequate laboratory time for specimen processing, which takes approximately 1–2 hours. Following excision, the parathyroid gland is dissected with a #10-blade scalpel into 30–40 pieces of uniform 2 × 2 mm within chilled sterile saline. The parathyroid tissue is never placed directly onto ice. Then, 15–20 small fragments are drawn up into a 1-mL tuberculin syringe. Ten milliliters of the patient's blood is collected to be used for freezing media. Specimen dissection in the operating room ideally occurs within 15 minutes of excision. The specimen is then immediately transported to the laboratory, ideally within a 5- to 10-minute walking distance of the operating room. Any transported and cryopreserved parathyroid tissue is first histologically confirmed by frozen section to be hypercellular parathyroid tissue to avoid cryopreservation of nonparathyroid tissue or parathyroid cancer. If processing will be delayed, the specimens can be placed at 2°C–8°C. The patient's blood specimen is centrifuged at 1,600 rpm for 5 minutes to separate the serum from the red blood cells. The isolated serum (1 mL) is used as part of the freezing media, in addition to 8 mL Roswell Park Memorial Institute (RPMI) 1640 solution and 1 mL dimethyl sulfoxide. Under a sterile hood, approximately ten parathyroid tissue fragments are transferred into a cryovial, and 1 mL of freezing media is added dropwise by a laboratory technician using sterile technique. The cryovials are slowly cooled before being transferred into a liquid nitrogen freezer for long-term storage by placing in a –20° C freezer for 15 minutes, then in a –50°C freezer for 15 minutes, followed by a vapor-phase nitrogen storage tank for two 24-hour cycles. Finally, they are submerged in a liquid-phase nitrogen storage tank for long-term storage. Cryopreservation allows storage of parathyroid tissue for at least 2 years, without compromise in cell function.[3]

Autotransplantation

The cryopreservation laboratory is notified the day prior to surgery, which allows time to determine the quantity of parathyroid tissue to thaw. The parathyroid tissue is

gradually thawed. A water bath is warmed to 37° C. A mixture of RPMI 1640 (90%) and serum substitute supplement (10%) is added to a centrifuge tube and placed in the water bath. First, 0.5 mL of warmed RPMI-SSS mixture is added to the cryovial and allowed to sit at room temperature for 5 minutes. Next, 1 mL of freezing media is removed and replaced with 1 mL of warmed RPMI-SSS and allowed to sit at room temperature for 5 minutes. This step is repeated two more times. Finally, the tissue fragments are resuspended in 1 mL RPMI 1640 in a new centrifuge tube. The parathyroid tissue fragments are then delivered to the operating room, where the surgeon transfers the fragments to a sterile specimen cup and dilutes them with sterile saline. Next, the parathyroid tissue fragments are reimplanted into the patient's nondominant forearm under local anesthesia. To do this, a 3-cm incision is made over the brachioradialis, and several small pockets are made in this muscle using blunt dissection. One to two fragments are placed into each pocket. The implants are marked with a surgical clip. Postoperatively, the patient's serum calcium and PTH levels are monitored weekly at first, then every 1–2 months on a case-by-case basis, and eventually every 3–6 months. Calcium supplementation was weaned as tolerated.

RESULTS

During the study period, >2,000 parathyroid operations were performed, 630 specimens were preserved (30%), and 9 of those were reimplanted (1.5% of cryopreserved tissue specimens). Of the nine patients requiring parathyroid reimplantation after their original parathyroid surgery, all achieved correction of hypocalcemia and improvement in detectable PTH levels. All patients had some symptomatic relief, with the majority experiencing complete symptomatic relief (67%). All were able to discontinue taking calcitriol except the patients receiving ongoing hemodialysis, for whom this was part of their dialysis protocol. The majority of patients were able to discontinue high-dose calcium supplementation (78%).

STUDY LIMITATIONS

One of the major limitations of this article is the small sample size of autotransplanted parathyroids, as well as the retrospective nature of this study. Other study limitations include that it was conducted at a single center and there was no economic analysis performed.

STUDY IMPACT

Parathyroid autotransplantation was first described by Halsted in 1907.[6] Parathyroid cryopreservation with the potential for delayed autotransplantation was first utilized in 1974 by Wells et al. as an alternative to immediate autotransplantation.[7] However, the indications and protocols for cryopreservation are highly variable among different institutions. This has resulted in variable rates and outcomes after delayed autotransplantation. Given the variability of outcomes, it has been suggested that a universal protocol that addresses how the resected tissue is transported, prepared, stored, thawed, and reimplanted may result in improved success rates of delayed

autotransplantation. This article outlines a standardized method for parathyroid cryopreservation that demonstrated successful autotransplantation of all reimplanted parathyroids.

RELEVANT ADDITIONAL STUDIES

Following parathyroid surgery, the complication of permanent hypoparathyroidism has significant negative impacts on the patient, including reduced quality of life, expensive lifelong medication supplementation, frequent laboratory testing, and the potential for frequent hospital admissions. In addition, the persistent absence of parathyroid hormone has long-term systemic effects on the body, such as the development of osteoporosis, premature cataracts, cardiac dysfunction, and neurologic dysfunction.

Parathyroid autotransplantation can correct post-parathyroidectomy hypocalcemia; however, the reported success of autotransplantation has been highly variable. Previous studies have reported fully functioning parathyroid autografts between 10% and 100% of the time (see Table 40.1). Due to the low rate of fully functional grafts in some studies, it has been suggested that the practice of parathyroid autotransplantation be abandoned altogether. However, the high variability in outcomes may be secondary to lack of a universal protocol for parathyroid autograft processing, handling, and storage, as suggested by Shepet et al.[8] This landmark study outlines a simplified technique that is easy to adapt in a typical hospital-based setting and achieves viable parathyroid tissue storage with successful reimplantation rates.

In addition, the practice of parathyroid cryopreservation has been criticized for the low utilization of cryopreserved tissue. Previous studies have reported that between 0.9% and 12.2% of cryopreserved specimens were autotransplanted [Caccitolo et al. (11.5%),

Table 40.1 Summary of studies reporting outcomes of parathyroid autotransplantation following cryopreservation

Study	Rate of Cryopreservation	Rate of Autotransplantation	Number of Autotransplants	Fully Functional Graft
Saxe et al. (1982)[9]	NS	NS	12	50%
Wagner et al. (1991)[10]	NS	NS	25	64%
Herrera et al. (1992)[3]	NS	NS	12	17%
Caccitolo et al. (1997)[11]	3.6% (112/3080)	11.6% (13/112)	13	23%
Feldman et al. (1999)[12]	NS	NS	26	31%
Cohen et al. (2005)[4]	NS	NS	34	40%
Borot et al. (2010)[13]	NS	NS	20	10%
Schneider et al. (2012)[14]	NS	NS	7	100%
Shepet et al. (2013)[8]	NS	NS	4	25%
Agarwal et al. (2013)[15]	NS	NS	9	100%
Total			**162**	**46%**

Abbreviations: NS, not specified.

Note: Rate of cryopreservation represents the percent of patients who underwent cryopreservation following parathyroidectomy in the study. Rate of autotransplantation represents the percent of cryopreserved specimens that were eventually autotransplanted. Fully functional graft is defined as an asymptomatic patient with normal biochemistry, not requiring any supplemental calcium or vitamin D

Cohen et al (7.8%), Borot et al (2%), Schneider et al (12.2%), Shepet et al (0.9%)]. Given that only a minority of patients require reimplantation, some have suggested that the cost of cryopreservation is not justified. However, autotransplantation offers an enduring cure for patients who would otherwise have limited improvement of permanent hypocalcemia and serves as a source for allogenic transplantation.[16]

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Chapter 41

Autofluorescence

Review by John Phay

Landmark Paper

INTRAOPERATIVE PARATHYROID AUTOFLUORESCENCE DETECTION IN PATIENTS WITH PRIMARY HYPERPARATHYROIDISM

Squires MH, Jarvis R, Shirley LA, Phay JE. *Ann Surg Oncol.* 2019;26(4):1142–1148. doi: 10.1245/s10434-019-07161-w

RESEARCH QUESTION/OBJECTIVES

The discovery that the parathyroid glands possess a natural autofluorescence in the near infrared (NIR) spectrum was based on a specifically designed research probe.[1] Only later was it appreciated that the spectral fluorescence pattern of parathyroids is similar to indocyanine green, which is the most commonly used fluorescence-guiding agent in surgery. This led to investigations by a variety of groups using camera- and probe-based systems that showed NIR systems could improve surgeon intraoperative identification of parathyroid glands. Initial feasibility studies were composed primarily of experiences with thyroid surgeries, where normal glands are identified and left in place without pathological confirmation, with a few small studies including a mixed cohort of thyroid and parathyroid operations. The primary aim of this study was to analyze the utility of autofluorescence in patients with primary hyperparathyroidism in a mixed-method form, where diseased glands are resected and confirmed pathologically, to quantitate autofluorescence intensity to potentially correlate with clinical variables, and to analyze surgeons' subjective opinion on identification and usefulness.[2]

STUDY DESIGN

A mixed-methods study of in situ and ex vivo NIR imaging performed on patients' parathyroid glands undergoing surgery for treatment of primary hyperparathyroidism using a commercially available handheld camera by two experienced surgeons. Post hoc image quantification and analysis were performed and correlated with clinical variables. Surgeon's confidence in parathyroid gland identification both with and without NIR imaging, as well as the surgeon's opinion of its utility, was also collected and evaluated.

SAMPLE SIZE

Fifty-nine primary hyperparathyroid patients undergoing surgery in the practice of two endocrine surgeons with a total of 69 resected parathyroid glands.

 DOI: 10.1201/9781003196211-41

INCLUSION/EXCLUSION CRITERIA

Only consecutive patients undergoing surgery for sporadic primary hyperparathyroidism were included. Patients with hereditary or secondary/tertiary hyperparathyroidism were excluded.

INTERVENTION OR TREATMENT RECEIVED

Using a sterilely draped handheld camera (PDE-Neo II, Mitaka, Tokyo, Japan), images in both ambient light and NIR mode were obtained initially during neck exploration (in situ) and of resected parathyroid glands (ex vivo). After the surgery, the surgeon reported their confidence in parathyroid identification both with and without NIR imaging, as well as whether NIR camera utilization helped identify glands or rule out suspected tissue as not being of parathyroid origin.

RESULTS

The surgeons reported that NIR camera use improved their confidence in parathyroid identification from an average of 4.1 (scale from 1 to 5) to 4.4 (+0.3, $p = 0.003$). Frozen section was routinely performed by the surgeons but was not performed in 29% of cases due to confidence in parathyroid gland intraoperative identification. Use of the camera helped identify a parathyroid gland in 12 of the 59 (20%) cases and helped rule out soft tissue candidates as not being parathyroid in 9 (15%) cases. Quantification of in situ autofluorescent images noted that parathyroids (75.9 ± 21.3) were scored significantly higher than either thyroid (61.1 ± 17.4) or adjacent soft tissues (53.3 ± 19.2) ($p < 0.001$ for both). The mean parathyroid autofluorescence ex vivo was higher (89.7) than in situ (75.9) ($p < 0.001$). The ratio of in situ parathyroid/thyroid autofluorescence was associated with parathyroid gland weight and volume. Preoperative parathyroid hormone (PTH) or calcium levels were not associated with mean parathyroid autofluorescence intensity.

STUDY LIMITATIONS

The study was a single institutional study carried out by two endocrine surgeons. One of the end points of the study was a subjective parameter based on the surgeon's opinion of their confidence in parathyroid identification as well as whether the system helped during the dissection. The study is limited by the relatively small numbers of patients and resected parathyroid glands. Quantification was performed by taking measurements from areas of equal dimensions (10×10 pixels) from the tissue's brightest areas. Even though this was performed in duplicate in a blinded fashion, selection of the area was subjective. This method also doesn't account for autofluorescence variability within the gland. Quantification was performed after the surgery, and therefore was not useful in real time for the surgeon during the operation. Finally, this study did not address whether use of the system improved surgical outcomes.

STUDY IMPACT

This was the first study to focus on the utility of NIR imaging during parathyroid surgery, where resected glands were pathological. This was also the first study to limit

the evaluation to only resected glands. An inherent limitation of prior studies was to include parathyroid glands that were left in situ, which are not confirmed pathologically. Although most of the initial studies in this field were performed by experienced surgeons, they are limited by this lack of tissue confirmation. This study also provided quantification of parathyroid autofluorescence using a camera system. Prior fluorescence quantification was performed in studies primarily using a probe, helping confirm the correlation between the two different types of systems. This was also the first study using this specific commercially available system, demonstrating that multiple systems are able to identify parathyroid NIR autofluorescence. Finally, the study collected in real time the surgeons' opinion on identification and usefulness, enabling a mixed-methods approach for analysis, finding that these experienced surgeons reported this technology helpful during parathyroid operations.

RELEVANT ADDITIONAL STUDIES

Intraoperative parathyroid gland identification has remained a challenge. During parathyroidectomies, in up to 10% of cases, not all pathological glands are removed, resulting in disease persistence and operative failure.[3] Several other studies published around the same time examined the feasibility of detecting parathyroid NIR autofluorescence. One of the first studies used a commercially available camera system, the Fluobeam 800 camera (Fluoptics, Grenoble, France).[4] First, they confirmed autofluorescence ex vivo on normal parathyroids in 28 specimens, even showing that the autofluorescence was still present after 24 hours of formalin fixation in 3 specimens, with no decrease in their fluorescence intensity. Intraoperatively, the camera was found to have a sensitivity of 98.8% in 35 patients. Another early study from Germany using a modified Karl Storz camera in 25 patients showed that parathyroids had substantial NIR autofluorescence compared to thyroid tissue, lymph nodes, and adipose tissue.[5] This study did include 21 resected glands, but did not find a difference between normal glands and adenomas. They found the system was clinically helpful in two cases: in one case tissue localized preoperatively by sestamibi scan was found intraoperatively not to have autofluorescence and later confirmed as being thyroid tissue, and in a second case an inferior parathyroid gland was identified by its autofluorescence during a central neck dissection. One of the first studies to focus on parathyroidectomies examined the utility of NIR autofluoresence in 98 patients undergoing surgery for primary and secondary hyperparathyroidism also using the Fluobeam 800 camera.[6] Fluorescence intensity was subjectively recorded by the surgeon as "low, medium or high." The authors found 61% of parathyroids had a high autofluorescence signal, and patients with primary hyperparathyroidism had significantly more glands with high intensity (68% vs. 34%) compared to secondary hyperparathyroidism cases. This has been the only study which reported a statistically significant correlation between preoperative serum calcium (and PTH in secondary hyperparathyroidism) and fluorescence intensity. The study is limited by the lack of quantification of autofluorescence signal intensity. The authors concluded that routine use of the camera was not justified, since they found that nearly 10% of parathyroid glands did not emit autofluorescence, and they were not able to identify three missing glands; therefore the technology was not likely to improve cure rates for hyperparathyroidism. One of the first studies to examine specifically the

differences in autofluorescence between normal and diseased glands was reported by the Cleveland Clinic, also using the Fluobeam camera, but in 50 patients with primary hyperparathyroidism undergoing a bilateral neck exploration.[7] Fluorescence intensity was calculated using ImageJ software (Rasband, W.S., ImageJ, U.S. National Institutes of Health, Bethesda, Maryland, USA) comparing the parathyroid to background tissue (excluding the thyroid), and hyperfunction of the gland was determined by intraoperative PTH fall using the Miami criteria. They found a significantly lower fluorescence intensity with hyperfunctioning glands compared to normal functioning glands (1.8 vs. 2.6, respectively). Hyperfunctioning glands were also found to have a more heterogenous fluorescence pattern than normal functioning glands. They did not find any correlation with preoperative calcium and PTH levels. Takeuchi et al. compared autofluorescence signal intensity of 24 glands both in situ and ex vivo and found glands from patients with primary hyperparathyroidism had significantly higher autofluorescence intensity than for secondary hyperparathyroidism (5.47 ± 7.4 vs. 0.99 ± 0.31 in situ, respectively; $p = 0.04$).[8] In a study of 23 patients with primary hyperparathyroidism, Demarchi et al. found the pathologic glands had a heterogenous fluorescence pattern with 74% of the specimens having a bright "cap" generally corresponding to a normal histological rim of parathyroid tissue.[9] Using a probe instead of a camera system, Law et al. published their experience in patients with primary hyperparathyroidism.[10] In 22 patients, they found that in situ adenomas (4.38) and ipsilateral normal glands (6.17) had a significantly higher autofluorescence intensity ratio (compared to thyroid) than surrounding tissues. The probe was able to detect parathyroid autofluorescence up to a distance of 10 mm in saline and 6 mm though a clear solid material.

In summary, although relatively recently discovered, parathyroid NIR autofluorescence has gained significant interest as a possible tool for intraoperative parathyroid gland detection during parathyroid surgery, which has previously been comprehensively reviewed.[3] Using both camera- and probe-based systems, multiple groups have demonstrated that NIR technology can help identify parathyroids during parathyroidectomy. Further investigation is needed to help clarify if this technology can help distinguish normal from abnormal glands, as well as differentiate different pathological subtypes. Much larger studies are required to determine if this technology can ultimately improve patient outcomes.

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CHAPTER 42

Normocalcemic Primary Hyperparathyroidism

Review by Samir Damji and Adrian Harvey

Landmark Paper

IS PARATHYROIDECTOMY SAFE AND EFFECTIVE IN PATIENTS WITH NORMOCALCEMIC PRIMARY HYPERPARATHYROIDISM?

Traini E, Bellantone R, Tempera SE, Russo S, Crea C, Lombardi CP, Raffaelli M. *Langenbecks Archives Surg.* 2018;403(3):317–323. doi: 10.1007/s00423-018-1659-0

RESEARCH QUESTION/OBJECTIVES

Normocalcemic primary hyperparathyroidism (nPHPT) was first described in the 1990s.[1,2] It is characterized by normal total and ionized serum calcium concentrations in the presence of consistently elevated parathyroid hormone (PTH) levels. While the entity is widely recognized, the authors note that it has yet to be fully characterized, with no consensus for recommending either medical or surgical treatment. The primary purpose of this landmark study was to compare the clinical, biochemical, and pathological phenotypes of patients diagnosed with normocalcemic and hypercalcemic primary hyperparathyroidism (PHPT). Secondarily, the authors sought to describe the clinical outcomes of patients undergoing surgery for nPHPT.

STUDY DESIGN

Retrospective, single-center cohort study of patients undergoing parathyroidectomy for PHPT between 1998 and 2016 at the Agostino Gemelli University Hospital, Rome, Italy. The study population was divided into two groups: Normocalcemic patients (Group A) and hypercalcemic patients (Group B). Primary outcome measures were clinical, biochemical, surgical, and pathological data. Secondary outcome measures were clinical and biochemical follow-up data for the normocalcemic patients (Group A). Comparative analysis was performed between the two groups. Chi-squared test was used for categorical variables, and *t* test was used for continuous variables.

SAMPLE SIZE

The authors identified 899 patients operated on for PHPT at a single institution between 1988 and 2016. After applying exclusion criteria, there were 731 patients with sporadic

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PHPT who underwent parathyroidectomy. A total of 154 patients were classified in Group A and 577 patients in Group B.

INCLUSION/EXCLUSION CRITERIA

Patients were excluded if they had a serum creatinine above the normal range (0.7–1.2 mg/dL) or incomplete preoperative data. The inclusion criteria for Group A were elevated PTH level, normal albumin-adjusted total serum calcium, no vitamin D deficiency, exclusion of those with impaired renal function, medication effects, or concomitant malabsorption diseases.

INTERVENTION OR TREATMENT RECEIVED

Preoperative localization with US and MIBI-SPECT was performed on all patients. Patients with concordant imaging underwent focused unilateral exploration and parathyroidectomy with a standard approach or a minimally invasive video-assisted approach. Equivocal/negatively localized patients underwent bilateral neck exploration (BNE). Intraoperative PTH monitoring was used in all cases, utilizing the validated Rome criteria to assess for successful excision of all hyperfunctioning glands.[3]

RESULTS

Seven hundred and thirty-one patients were included in the analysis (Group A, $n = 154$ and Group B, $n = 577$). There was no significant difference in demographic data or symptomatic presentation between the groups. The mean serum PTH and albumin-adjusted calcium levels were significantly higher in Group B, (252.0 ± 320.7 pg/mL and 11.6 ± 1.0 mg/dL [Group B] vs. 151.7 ± 112.0 pg/mL and 10.0 ± 0.5 mg/dL [Group A]; $p < 0.001$). There was no significant difference in overall accuracy of preoperative localization studies for either group. The rate of multigland disease (MGD) was significantly higher in Group A than in Group B (13.0 vs. 6.8%, $p < 0.05$). More BNEs were performed in Group A (53.9% vs. 44.2% $p < 0.05$). The authors do not state how many patients underwent intraoperative conversion from a unilateral to bilateral surgical approach. In patients with MGD, localizations were concordant for single-gland disease in 50% in Group A and 33.3% in Group B. On pathology, of those patients with MGD, 45% had double adenomas and 55% had hyperplasia. Biochemical follow-up was available for 96/154 patients in Group A and showed that 3.1% of patients had evidence of persistently high PTH at a mean follow-up of 72.9 ± 46.8 months. Clinical follow-up was available in 42/69 patients in Group A who had initially presented with symptoms and/or target organ damage, 37/42 patients reported subjective improvement in their clinical status. In addition, of 12 patients with follow-up DEXA scans, 6 patients showed stability and 5 showed improvements in bone mineral density (BMD). Of ten patients with preoperative kidney stones who had undergone a postoperative renal ultrasound, four patients (40%) showed complete resolution of stones.

STUDY LIMITATIONS

Although this study provided some valuable insights into this hyperparathyroidism phenotype, the findings must be understood within the context of the limitations of the study design. The retrospective nature of this study with the potential introduction of bias must be considered. Additionally, there is no control comparative group with patients undergoing nonoperative management to elucidate the natural history of the disease process. In this study, Traini et al. also did not incorporate ionized calcium levels to define and distinguish normocalcemia from classical hyperparathyroidism. This major limitation may have unduly overestimated the number of patients with nPHPT, potentially significantly affecting the results and their interpretation. Wang et al., in their single-institution, retrospective review of patients undergoing parathyroidectomy for PHPT treatment, found that 12% of patients had consistently normal serum calcium.[4] Of these patients, 86% had high ionized calcium levels, therefore requiring reclassification into a hypercalcemic cohort. Wang et al., along with a consensus statement from the Fourth International Workshop on the Management of Asymptomatic Primary Hyperparathyroidism, have recommended measuring ionized calcium to identify patients with nPHPT.[5] The limited follow-up data presented limits the generalizability of the findings. Follow-up data was only provided for Group A and therefore no further comparisons can be made; additionally this was on a small subset of patients, with 10 patients undergoing renal ultrasound and 12 patients undergoing DEXA scans.

STUDY IMPACT

The authors observed a significantly higher rate of MGD in the normocalcemic patient cohort compared to the cohort with the hypercalcemic phenotype. However, this study also demonstrated a significant rate of falsely concordant localization in the MGD group. The authors identified that localization imaging may be misleading in up to half of patients with nPHPT and MGD. This further emphasizes the importance of patients undergoing parathyroidectomy by experienced surgeons, while utilizing adjuncts such as intraoperative PTH monitoring to achieve a cure and reduce the need for reoperation.

In nPHPT patients with evidence of end-organ effects and follow-up data, parathyroidectomy proved to be safe and effective in ameliorating the end-organ effects. Postoperative DEXA scan data showed improvement in BMD in 41.7% of patients and stability in 50% of patients, while postoperative renal ultrasound demonstrated that 40% of patients had no further evidence of nephrolithiasis. The high rate of double adenomas identified within the normocalcemic patients would also suggest that nPHPT is a distinct clinical entity rather than an early-stage presentation of the classical hypercalcemic hyperparathyroidism phenotype that has been proposed by others. Although the natural history of nPHPT remains unclear, Traini et al. have provided us with a better understanding of the surgical management and provided a glimpse into the postoperative clinical and biochemical outcomes of this phenotype.

Despite an increasing number of patients being identified with this subtype of PHPT, much remains unknown. Nearly all patients with nPHPT are diagnosed in the setting

of kidney stones or metabolic bone disease, and therefore available evidence is from a referral population where selection bias has occurred. We therefore have a poor understanding of the management of mild, asymptomatic patients with nPHPT. The available data for surgical management and the associated outcomes is difficult to interpret due to decreased accuracy of localization studies and increased risk of MGD. Future prospective studies are needed to identify optimal diagnostic criteria and to better understand the role of surgery in these patients.

RELEVANT ADDITIONAL STUDIES

The limited data available regarding surgical management and clinical outcomes suggests that patients undergoing surgery have objective improvement in BMD scores.[6,7] Koumakis et al., in a study of 39 nPHPT patients, demonstrated BMD improvements both at the lumbar spine (2.3% ± 5.0%; $p = 0.016$) and femoral neck (1.9% ± 5.7%; $P = 0.048$) 1 year after parathyroidectomy.[6] Similarly Sho et al. showed that normalization of serum PTH was associated with a mean BMD increase of 5.6% at the site of lowest preoperative *t*-score on a DEXA scan.[7] Renal outcomes in patients undergoing surgery for nPHPT is less well understood, with a paucity of published data. Grimelius et al. published a series of 80 patients with nPHPT, demonstrating that 72% were stone-free at a mean follow-up of 3.5 years.[8] This was mirrored by Traini et al.'s findings of 40% of patients being stone-free during follow-up. Cardiovascular dysfunction is a manifestation of PHPT, and the data surrounding improved outcomes in NPHT is limited. Beysel et al. evaluated the association of parathyroidectomy and cardiovascular risk factors in nPHPT patients and found improvement in cardiovascular risk scores with a significantly reduced blood pressure, insulin resistance, and cholesterol levels.[9]

The increased incidence of MGD within nPHPT patients is very relevant and an important consideration when surgical planning is undertaken. Pandian et al., in a CESQIP multi-institutional database analysis, reported that nPHPT patients were more likely to have hyperplasia (43.1% vs. 21.9%) and less likely to have a single adenoma (47.5% vs. 73.3%) compared with patients with hypercalcemic PHPT.[10] Thus a focused or unilateral approach is less likely to be successful in this context, and the use of operative adjuncts such as interoperative PTH is of paramount importance. Lim et al. demonstrated a higher risk of conversion from targeted surgery to BNE in nPHPT patients compared with those with hypercalcemic disease (13% vs. 4%).[11] Both Dawood et al. and Cusano et al. in their comprehensive reviews outline the biochemical and surgical outcomes in a small number of studies of patients with nPHPT who underwent surgery.[12,13] However, both commented that the clinical benefits of medical and surgical interventions in nPHPT patients, while poorly understood, may be effective in ameliorating complications, but the condition requires further large-scale studies with extended follow-up.

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CHAPTER 43

Normohormonal Primary Hyperparathyroidism

Review by Mechteld C. de Jong and Sheila M. Fraser

Landmark Paper

THE PHENOTYPE OF PRIMARY HYPERPARATHYROIDISM WITH NORMAL PARATHYROID HORMONE LEVELS: HOW LOW CAN PARATHYROID HORMONE GO?

Wallace LB, Parikh RT, Ross LV, Mazzaglia PJ, Foley C, Shin JJ, Mitchell JC, Berber E, Siperstein AE, Milas M. *Surgery.* 2011;150(6):1102–1112. doi: 10.1016/j.surg.2011.09.011

RESEARCH QUESTION/OBJECTIVES

Primary hyperparathyroidism (PHPT) is the most common cause of hypercalcemia in the general population.[1] Its diagnosis is usually based on an abnormal biochemical profile that is characterized by an inappropriately elevated serum parathyroid hormone (PTH) level in the setting of high serum calcium.

However, not all patients with PHPT display this biochemical profile, as there is data to support the existence of normocalcemic hyperparathyroidism,[2,3] or an inappropriately normal (i.e., nonsuppressed) PTH level in the setting of hypercalcaemia.[4,5] Less is known about those patients presenting with a biochemical profile consisting of high calcium levels associated with low-normal levels of PTH. Therefore, patients presenting with such laboratory findings could potentially evade diagnosis and referral for surgery.

The aim of the landmark paper was therefore to characterize this subgroup of hyperparathyroid patients referred to as having *normohormonal primary hyperparathyroidism* (NHPHPT).

STUDY DESIGN

This study was a retrospective analysis of a subgroup of patients with preoperative PTH levels below (NHPHPT) and above (classical PHPT) the upper limit of the normal reference range (i.e., 60 pg/mL) taken from a prospectively maintained database of patients undergoing bilateral neck parathyroid exploration (BNE) for treatment of PHPT.

SAMPLE SIZE

A group of 46 patients with NHPHPT was compared to a group of patients with classical PHPT ($n = 916$).

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INCLUSION/EXCLUSION CRITERIA

A group with NHPHPT ($n = 46$; 5%) was selected from all patients who underwent BNE for PHPT at a single institution between January 2005 and November 2010 ($n = 843$), excluding those with multiple endocrine neoplasia syndrome. This group was composed of patients who had preoperative PTH values within the normal reference range (10–60 pg/mL) and was further subdivided into three groups, based on the results of their preoperative PTH-measurements (I: All <40 pg/mL: $n = 7$; II: All <60 pg/mL: $n = 19$; and III: Few >60 pg/mL: $n = 20$). A comparison group of patients with classical PHPT ($n = 916$) was evaluated, including only patients with PTH levels above the normal reference range. This group was a historical comparison group from an earlier study by the same authors.[6]

INTERVENTION OR TREATMENT RECEIVED

The study describes the biochemical workup utilized to confirm the diagnosis of PHPT, which consisted of measuring serum total and ionized calcium, PTH, 25-OH vitamin D, and 1,25-OH vitamin D. Generally two complete laboratory sets that showed the presence of hypercalcemia with an elevated PTH were required to confirm the diagnosis of PHPT. Due to the diagnostic dilemma of NHPHPT, i.e., absence of elevated PTH, these patients underwent additional testing in the form of multiple measurements of serum PTH values. Moreover, 24-hour urinary calcium and creatinine levels were obtained from all patients to identify any with a familial hypocalciuric hypercalcemia (FHH) diagnosis. Following the confirmation of the biochemical diagnosis of PHPT, localization studies were obtained, including a surgeon-performed ultrasound scan (US) and a I-123 subtraction 99Tc-sestamibi SPECT/CT scan ("MIBI scan").

Overall, all patients were planned to undergo BNE, with focused parathyroidectomy performed only in selected cases (e.g., reoperations, presence of medical comorbidity, and those participating in a study protocol assessing focused surgery). Among those cases with NHPHPT, BNE was performed in 42 (91%) patients versus focused exploration in the remaining 4 (9%) patients. For those with classical PHPT, all ($n = 916$; 100%) underwent BNE. During surgery, intraoperative measurement of PTH (ioPTH) was used during both bilateral and focused operations, following the Miami protocol.[7]

RESULTS

All patients ($n = 46$) within the NHPHPT group had hypercalcemia. Upon assessing the PTH level, three subgroups could be identified: I: All PTH measurements <40 pg/mL: $n = 7$; II: All <60 pg/mL: $n = 19$; and III: Few >60 pg/mL: $n = 20$. The disease was incidentally discovered in 74% of NHPHPT cases versus 51% among those with classical PHPT ($p < 0.05$). However, retrospectively, 70% of NHPHPT cases had at least one symptom of PHPT. In the majority, these were bone-related symptoms (50%), while almost one-fifth (17%) had a history of renal stones, and more than one-third (37%) had reported at least one neuropsychiatric symptom (e.g., fatigue, irritability, poor concentration, declining memory, or altered mood).

During the operation, a single parathyroid adenoma was found in comparable proportions among those with NHPHPT (74%) and those with classical PHPT (68%) ($p > 0.05$), with a similar total abnormal gland volume (NHPHPT: Mean 786 ± 100 mm^3 vs. classical PHPT: Mean 717 ± 81 mm^3, respectively; $p > 0.05$).

While the intent of the study was not to determine the accuracy of ioPTH for management of NHPHPT versus classical PHPT, the included data did show that in 82% (36 out of 44 in whom ioPTH was used) with NHPHPT, an elevated pre-resection ioPTH was found. As only those patients ($n = 20$; 43%) in subgroup III had a few preoperative PTH measurements showing an elevated PTH (i.e., >60 pg/mL), the ioPTH findings were further evaluated in four patients. Specifically, these patients had repeated ioPTH measurements taken from multiple venipuncture sites both in central and peripheral locations. Importantly, in all four patients, the pre-resection values were elevated and similar at all sites, and the postresection values were also comparable between sites. Moreover, a 50% decline in ioPTH levels was seen in 34 out of 36 patients (94%) with elevated pre-resection ioPTH and also in 7 out of 8 (88%) with normal pre-resection ioPTH (93% of total).

At time of last follow-up (median 8.9 months, range 0.5–62), 44 patients with NHPHPT (96%) were cured, with both serum calcium and PTH levels within the normal range. One patient (2%) had persistent disease, with an elevated serum calcium level but a normal PTH (39 pg/mL). Another patient (2%) developed recurrent disease, again with an elevated serum calcium level but a normal PTH (23–53 pg/mL). Importantly, while no patients experienced symptomatic hypocalcemia, two patients (4%) did develop chronically low PTH levels, with normal calcium levels.

STUDY LIMITATIONS

This study is a retrospective cohort study, comparing a subgroup of NHPHPT patients with a larger historical cohort of patients with classical PHPT. There are limitations inherent in the nature of this retrospective study design, such as the potential for missing data or uncontrolled confounding factors. Moreover, while this was, at the time, the largest cohort of NHPHPT patients reported, the study population was relatively small, possibly precluding further analyses. Furthermore, there could have been a selection bias in the cohort, as it only consisted of patients who underwent surgery. Therefore the characteristics of the NHPHPT patient population overall could differ from the study group.

In this landmark paper the possibility that in the NHPHPT group the parathyroid glands could have been normal at surgery is mentioned, although this was not actually found to be the case in the study population. This should be viewed as a surrogate for the absence of robust biochemical criteria for the diagnosis of NHPHPT. No clear (tailored) biochemical workup was described for the included group of NHPHPT to avoid an incorrect diagnosis. It is unclear why 82% of the NHPHPT group had elevated pre-resection ioPTH levels, when the vast majority of PTH assays in this group had been in the normal range on preoperative workup.

It is paramount for the laboratory testing in NHPHPT to be complete and conclusive and that the profile is present on multiple measurements. Moreover, although the calcium–creatinine ratio was used to exclude FHH, none of the patients underwent genetic testing for that condition. And lastly, while the study does give a very detailed overview of the patients who underwent surgery for NHPTPH, there is only very limited data on any additional testing these patients underwent to determine the potential underlying mechanism for NHPHPT.

STUDY IMPACT

The landmark paper is of importance, as it was one of the first to provide a systematic analysis of a relatively large cohort of NHPHPT patients and thereby raised awareness of this diagnosis. It confirmed previous reports of patients with this variant of PHPT consisting of hypercalcemia associated with normal levels of PTH.[8,9] It also showed that, compared to those with classical PHPT, patients with NHPHPT have similar symptoms, comparable findings at surgery, and similar long-term outcomes. This is of importance, as the general PHPT guidelines[5,10,11] cannot be fully applied to those presenting with the biochemical profile of NHPHPT. Therefore, these patients could be at increased risk of missed or delayed diagnosis and surgical treatment, leading to an increased risk of complications from PHPT.

At the time of publication of the selected landmark study, there were no evidence-based guidelines for the management of this challenging patient subgroup, and thus the data from this study provided some important early insights, allowing surgeons to proceed more confidently in recommending parathyroidectomy. The data presented in the study offered a framework to support counseling of patients diagnosed with NHPHPT, for instance, in terms of the potential benefits of surgery to halt the progression of the disease.

RELEVANT ADDITIONAL STUDIES

Since publication of this landmark paper,[12] reports of several cohorts of NHPHPT patients have been published, confirming its existence and further characterizing this PHPT patient subgroup.[13–16] A recent review comparing, among others, NHPHPT and classical PHPT, reported that the proportion of NHPHPT cases accounted for approximately 6–17% of PHPT patients[17] – although no exact requirement for a minimum biochemical workup was described. This proportion was even higher in a study by Applewhite et al.,[18] who reported on a larger cohort consisting of 116 patients with NHPHPT, representing almost a quarter (23%) of their total cohort with PHPT. Overall, recent reports that include relatively large proportions of PHPT patients with NHPHPT suggest that awareness of this variant has increased, and surgical referral may be undertaken more frequently.

While several recent publications support NHPHPT as a separate entity, there has been conflicting data emphasizing the need for further studies into this phenotype. For instance, while some studies suggest similar patterns of presentation in terms of

bone-related disease or renal stones,[14,19] others report that these complications are higher among those diagnosed with NHPHPT compared with classical PHPT.[17,18] This finding could be due to referral bias, though, as both symptoms could have been the reason for referral for treatment. In cases of end-organ damage, the decision to proceed to surgery is easier, but more still needs to be elucidated regarding surgical intervention in patients with more subtle symptoms from NHPHPT. Moreover, some groups reported comparable findings at surgery in NHPHPT and classical PHPT,[8,12] but more recent studies reported higher proportions of multiglandular disease and a lower total gland weight for NHPHPT patients,[18,19] suggesting the possible need for a more tailored surgical approach to this group, such as BNE with ioPTH.

The exact mechanisms underlying NHPHPT remain to be elucidated, with several theories having been proposed, including pulsatile secretion of PTH; secretion of an abnormal PTH hormone affecting its measurement but not its function; presence of unmeasured active PTH fragments; presence of circulating antibodies interfering with the assay; presence of another mediator of hypercalcemia (i.e., PTH-related peptide); increased peripheral tissue sensitivity to normal PTH; lower PTH setpoint; and anatomic barriers in local circulation around a parathyroid neoplasm.[9,13,20–25] Moreover, the selected landmark paper has proposed more potential mechanisms, namely variations or discrepancies arising from different assay manufacturers, venipuncture locations, or in collection and storage of samples.[12] None of these theories have thus far been established in larger studies and are generally lacking robust scientific evidence to support them. Conversely there are those who believe NHPHPT is an early diagnosis[14,26] and so could potentially represent a mild and early form of classical PHPT.

In conclusion, although awareness of NHPHPT has increased over recent years, leading to improved and earlier recognition, the entity remains incompletely characterized, and further, larger studies with longer-term follow-up are necessary. Moreover, the exact etiology remains to be elucidated, and a better understanding of NHPHPT is required. In addition, more robust criteria for biochemical workup and diagnosis of NHPHPT need to be established, as well as guidelines on when to operate on this group.

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Chapter 44

Recurrent Hyperparathyroidism

Review by Matilda Annebäck and F. Fausto Palazzo

Landmark Paper

18F-FLUOROCHOLINE PET/CT AND PARATHYROID 4D COMPUTED TOMOGRAPHY FOR PRIMARY HYPERPARATHYROIDISM: THE CHALLENGE OF REOPERATIVE PATIENTS

Amadou C, Bera G, Ezziane M, Chami L, Delbot T, Rouxel A, Leban M, Herve G, Menegaux F, Leenhardt L, Kas A, Tresallet C, Ghander C, Lussey-Lepoutre C. *World J Surg.* 2019;43(5):1232–1242. doi: 10.1007/s00268-019-04910-6

RESEARCH QUESTION/OBJECTIVES

Persistent or recurrent primary hyperparathyroidism (pHPT) requiring reoperative parathyroidectomy is challenging, and preoperative imaging is central to surgical planning. The usual paradigm of ultrasound (US) and sestamibi imaging followed by venous sampling has in recent times been added to by promising new imaging tools. The aim of this landmark paper was to assess the value of ^{18}F-fluorocholine (^{18}F-FCH) PET/CT and 4D-CT in reoperative patients with primary hyperparathyroidism.

STUDY DESIGN

Retrospective, cohort study from a tertiary, single-center institution. Data was collected from local health records.

SAMPLE SIZE

A total of 29 patients were included in the study. Out of these, 23 (79%) had undergone previous surgery for pHPT, 6 (21%) had surgery for thyroid goiter, and about a quarter had combined parathyroid and thyroid surgery.

INCLUSION/EXCLUSION CRITERIA

All patients referred for ^{18}F-FCH PET/CT for pHPT between January 2016 and December 2017 were included. Patients without previous neck surgery or with loss to follow-up were excluded.

INTERVENTION OR TREATMENT RECEIVED

All patients had US and technetium-99m sestamibi scintigraphy (^{99m}Tc-sestamibi) with or without SPECT/CT and ^{18}F-FCH PET/CT. Some patients underwent 4D-CT. The gold

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standard was defined as histology and/or US-guided fine needle aspiration (FNA) with parathyroid hormone (PTH) measurement. Imaging results were considered true positive (TP), true negative (TN), false positive (FP), or false negative (FN) according to surgery and/or FNA findings as a gold standard. On per-patient analysis, each patient was classified into two different categories: TP or FN.

RESULTS

4D-CT was performed in 20 (69%) patients. US and ^{99m}Tc-sestamibi were both negative or discordant in 21 (72%) patients. The gold standard was acquired for 32/39 foci in 27/29 patients. In total, 23 patients underwent surgery and 15 patients US-guided FNA. ^{18}F-FCH PET/CT and 4D-CT had sensitivities of 96% and 75% with a positive predictive value (PPV) of 77% and 80%, respectively. 4D-CT had a higher specificity than ^{18}F-FCH PET/CT. The study showed the superiority of ^{18}F-FCH PET/CT and 4D-CT compared to first-line imaging with US and ^{99m}Tc-sestamibi. However, the specificity of ^{18}F-FCH PET/CT and 4D-CT for localizing parathyroid disease was somewhat lower, presumably due to the take-up of the tracer by other structures.

STUDY LIMITATIONS

The study has some limitations that must be considered. It included a relatively small number of patients and not all patients underwent both ^{18}F-FCH PET/CT and 4D-CT, which could impact the results. Not all patients underwent surgery, so the impact of ^{18}F-FCH PET/CT on cure from pHPT in all 29 patients included in this study could not be established. The cases were heterogeneous, as some had previously undergone thyroid surgery, though the majority had undergone parathyroid surgery. Further studies have since been added to the literature, but still larger prospective quality studies are required.

STUDY IMPACT

This qualifies as a landmark paper because it was the first to scientifically evaluate the use of ^{18}F-FCH PET/CT and 4D-CT in reoperative patients with pHPT. Whereas others had investigated the performance of ^{18}F-FCH PET and 4D-CT in patients with pHPT in isolation, this article provided more controlled and precise information about the validity of ^{18}F-FCH PET and 4D-CT in patients with pHPT who had undergone prior neck surgery.

RELEVANT ADDITIONAL STUDIES

Persistent pHPT is defined as hypercalcemia within 6 months of parathyroid surgery, while recurrent pHPT is defined as hypercalcemia occurring after this watershed time point. Persistent pHPT is far more common than recurrent pHPT and is usually caused by a missed adenoma at the initial operation.[1] Even though ectopic adenomas are more common in a reoperative setting than in primary surgery, most missed adenomas are found in eutopic positions at reoperation.[2,3] Another reason for persistent disease is unrecognized

multiglandular disease. Patients with unlocalized disease on preoperative imaging have a higher risk of failure to cure and are also more likely to have multiglandular disease.[4,5]

The joint consensus guidelines of the American Head and Neck Society and the British Association of Endocrine and Thyroid Surgeons laid out the blueprint for the optimal management of patients requiring reoperative parathyroid surgery.[6] Once the diagnosis of pHPT is confirmed, a thorough review of the patient's medical history, previous workup, surgical notes, and histopathology is required. A possible family history of pHPT should be evaluated specifically. Furthermore, all patients considered for reoperative surgery should undergo laryngoscopy for assessment of their vocal cord function, since a vocal cord paralysis may alter the threshold for surgery.

Reoperative parathyroid surgery is associated with a higher risk of complications and is associated with a lower success rate than first-time surgery. Reoperative surgery can be challenging due to extensive scar tissue and distortion of the anatomy due to previous interventions. Data from the UK Registry of Endocrine and Thyroid Surgeons (UKRETS) has shown a six-fold increase in the risk of vocal cord palsy from reoperative parathyroidectomy compared to first-time surgery.[7] Permanent hypoparathyroidism rates of 3–13% are also described.[2,7,8] Given the increased risks, the potential benefit of cure of the hyperparathyroidism must be weighed against the possible adverse events of surgery. Moreover, reoperative parathyroidectomies should preferably be performed by experienced surgeons in high-volume centers. In these settings, reoperative parathyroid surgery has been shown to have an excellent outcome, with a cure rate of 95–100%, probably in part due to patient selection.[1,9,10]

Preoperative localization studies are essential for reoperative surgical planning in order to avoid the unnecessary risks of blind explorations in a field of scar tissue. Several imaging modalities can be used for this objective, such as US, ^{99m}Tc-sestamibi with or without SPECT/CT, 4D-CT, PET, and venous sampling. The availability of the different modalities will vary between sites and health systems.

The combination of US and ^{99m}Tc-sestamibi is usually the first choice for localization studies, and the combination has been shown to be superior to either method alone.[11] However, the rates of indecisive findings for first-line imaging has been reported to be as high as 63% in patients undergoing reoperative parathyroidectomy.[3] Although US is relatively inexpensive and safe, it is highly user-dependent and has limitations – in particular, in the identification of parathyroid glands present in posterior locations, parathyroids high in the neck, and low ectopic parathyroids within the mediastinum. The sensitivity for US after previous parathyroid or thyroid surgery varies from 61% to 74%, with a PPV of 72–93%.[1,2] US-guided FNA with PTH measurement of suspected parathyroid lesions may be valuable in the reoperative setting. The accuracy of ^{99m}Tc-sestamibi also decreases in patients with persistent/recurrent pHPT. The reported sensitivity varies widely and ranges between 33% and 89% with a PPV of 67–96%.[12–14] Several factors contribute to the lower rate of detection of hyperactive parathyroid glands in patients with persistent/recurrent pHPT, including a higher proportion of hyperplastic glands, presence of concurrent thyroid disease, and distorted anatomy with altered perfusion of the remaining glands.

If the results from first-line imaging studies are negative or discordant, further imaging is inevitably required. Second-line imaging can involve 4D-CT or PET. 4D-CT has been shown to be better than both US and ^{99m}Tc-sestamibi in localizing parathyroid disease in patients with recurrent or persistent pHPT, with a sensitivity of 77–88%.[15–17] An advantage of 4D-CT is its wide availability and its precise anatomical localization of the hyperfunctioning parathyroid. However, 4D-CT is associated with exposure to a higher radiation dose compared to ^{99m}Tc-sestamibi and PET, which can be problematic, especially for younger patients. Furthermore, the sensitivity for multiglandular disease is decreased on 4D-CT, although the method is reported to be more accurate in this setting than both US and ^{99m}Tc-sestamibi.[16]

Several PET tracers have been investigated for parathyroid localization, with ^{18}F-FCH and ^{11}C-methionine (MET) being the most studied. ^{11}C-MET PET has reported sensitivity rates between 77% and 88% in reoperative patients with persistent or recurrent HPT.[1] However, ^{11}C-labeled tracers have a short half-life, making the logistics of using them challenging and their availability limited. Over the past decade, ^{18}F-FCH tracers have been shown to be useful in locating hyperfunctioning parathyroids in patients with pHPT and no previous neck surgery.[18] In addition to this landmark paper, other studies have evaluated the use of ^{18}F-FCH PET/CT in patients with pHPT undergoing reoperative surgery.[19–21] Although these studies are retrospective and include small numbers of patients, ^{18}F-FCH PET/CT appears to show greater efficacy than 4D-CT in detecting hyperfunctioning parathyroids.[21]

If the noninvasive imaging is negative or inconclusive, selective venous sampling (SVS) and parathyroid angiography may provide valuable information.[22,23] SVS and angiography are technically difficult and require an experienced radiologist. The risk of complications is low but potentially severe, including vascular injury and stroke. Therefore, SVS and angiography should only be considered when noninvasive studies have failed to localize the hyperfunctioning parathyroid.

Operative adjuncts can be helpful and facilitate parathyroidectomy. There is a consensus supporting the use of recurrent laryngeal nerve monitoring in the reoperative setting.[6] Furthermore, many authors agree on the value of intraoperative PTH (IOPTH) in reoperative parathyroidectomy.[9,24,25] It would appear that, to date, no study has explored the relationship of surgeon volume and outcomes in patients undergoing reoperative parathyroidectomy, presumably because the evidence base for volume outcome in parathyroidectomy in general alone suffices. Indeed, higher surgical volume has been shown to increase the cure rate and lower the risk of persistent pHPT and complications in patients undergoing first-time surgery for pHPT.[26] Therefore, it is logical that surgeon volume and experience are important for the success rate in patients requiring reoperative surgery.

In conclusion, reoperative parathyroidectomy is challenging and associated with an increased risk of complications. This landmark article has demonstrated, in a preliminary way, the value of 4D-CT and ^{18}F-FCH in this challenging patient population. Larger studies, including cost-efficiency data, would provide important further information on the utility of these imaging methods.

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Chapter 45

Surgical Complications

Review by Neil Patel and Michael Stechman

Landmark Paper

PREDICTORS OF OPERATIVE FAILURE IN PARATHYROIDECTOMY FOR PRIMARY HYPERPARATHYROIDISM

Cron DC, Kapeles SR, Andraska EA, Kwon ST, Kirk PS, McNeish BL, Lee CS, Hughes DT. *Am J Surg*. 2017;214(3):509–514. doi: 10.1016/j.amjsurg.2017.01.012

RESEARCH QUESTION/OBJECTIVES

Aside from general complications such as hemorrhage, infection, and voice change, which are rare, failure to achieve normocalcemia is the most common adverse outcome following parathyroid surgery and has a reported incidence of 2–12%.[1–4] Persistent postoperative hypocalcemia is usually due either to the inability to find a parathyroid tumor because of the variability in parathyroid location or the failure of the surgeon to appreciate that, rather than single-gland disease, the patient has multigland disease (MGD).[5,6] Although variability of the parathyroid position in the neck is relatively common, such glands are usually found by the experienced parathyroid surgeon. Only in less than 1% of parathyroid operations will glands be found in congenitally ectopic locations such as high in the neck, in a retropharyngeal position, or in the chest.[5] Various approaches have been introduced to reduce the incidence of failed parathyroid exploration: preoperative localization with neck ultrasound; sestamibi scanning, lately with SPECT-CT; and the use of intraoperative parathyroid hormone (IOPTH) measurement (second-line imaging with 4D-CT or PET choline is used in some units when initial imaging does not reveal an adenoma or for patients with recurrent/persistent disease). Despite these interventions, even in expert centers, there remains a small number of patients in whom cure is not possible with first-time surgery.[7] This has led to the question as to whether there are other identifiable factors that may predict operative failure.[8] This landmark paper aimed to investigate the independent effect of demographics, preoperative disease severity, imaging and IOPTH results, and pathology findings as predictors of operative failure (persistent hyperparathyroidism) after parathyroidectomy.

STUDY DESIGN

A retrospective study of a prospectively maintained database of patients undergoing parathyroidectomy at a single North American tertiary care center between 1999 and 2014.

DOI: 10.1201/9781003196211-45

SAMPLE SIZE

A total of 2,239 patients undergoing parathyroidectomy for primary hyperparathyroidism.

INCLUSION/EXCLUSION CRITERIA

Included were patients who underwent parathyroidectomy during the study period. No age criterion was set, and it was not specified whether patients with concomitant thyroid surgery were included. Patients with secondary or tertiary hyperparathyroidism, reoperative parathyroidectomy, multiple endocrine neoplasia type 1, and a history of lithium use were excluded.

INTERVENTION OR TREATMENT RECEIVED

Variables identified by the authors as potential predictors of operative failure (age, sex, preoperative peak PTH, preoperative peak calcium, imaging localization, imaging correctness, four-gland exploration, IOPTH monitoring criteria met, number of glands excised, and total weight of glands excised) were assessed against the outcome of operative failure using univariate and multivariate logistic regression. The end point was operative failure, which was defined as persistent disease (postoperative calcium measurements persistently >10.2 mg/dL [2.54 mmol/L] or a single calcium >/11.0 mg/dL [2.74 mmol/L]) on postoperative calcium measurement or within 6 months after operation. PTH was not checked postoperatively and so did not contribute to the definition of persistent disease in this study.

Two statistical models were constructed (preoperative factors and preoperative combined with intraoperative factors). Area under the curve (AUC) analysis was used to assess the predictive ability of the model for operative failure against an internal training validation cohort.

RESULTS

Of the cohort, 67 patients (3%) were found to have persistent disease. Univariate logistic regression analysis identified the following variables to correlate with persistent hyperparathyroidism, identifying them as risk factors for operative failure: Multiple glands excised (odds ratio [OR] = 2.96, 95% confidence interval [CI]: 1.79–4.90, $p < 0.001$), four-gland exploration (OR = 2.44, 95% CI: 1.48–4.02, $p < 0.001$), and higher preoperative calcium (OR = 1.38 per unit increase, 95% CI: 1.03–1.83, $p < 0.028$).

The following factors were found to be associated with cure (protective): IOPTH criteria met (OR = 0.21, 95% CI 0.13–0.35, $p < 0.001$), larger weight of excised gland(s) (OR = 0.70 per two-fold increase, 95% CI: 0.59–0.82, $p < 0.001$), ultrasound and sestamibi both correct (OR = 0.23 compared to incorrect imaging, 95% CI: 0.09–0.61, $p < 0.003$), higher preoperative peak PTH (OR = 0.66 per two-fold increase, 95% CI: 0.48–0.91, $p < 0.011$) and ultrasound and sestamibi localizing and concordant (OR = 0.31 compared to no localizing imaging, 95% CI: 0.13–0.78, $p < 0.013$). Modeling for preoperative risk factors only and conducting multivariate analysis

resulted in two significant variables: Preoperative peak PTH (OR = 0.47 per two-fold increase, 95% CI: 0.30–0.74, $p < 0.001$) and calcium (OR = 2.01 per unit increase, 95% CI: 1.31–3.09, $p < 0.001$). When the model was assessed for its predictive value using a training and validation dataset, the AUC values were 0.71 (95% CI: 0.62–0.79) and 0.58 (95% CI: 0.46–0.70).

When modeling for combined patient and intraoperative factors, multivariate analysis identified the following variables as independently associated with persistent disease: IOPTH criteria being met (OR = 0.22, 95% CI: 0.11–0.44, $p < 0.001$), preoperative peak calcium (OR = 2.27, 95% CI: 1.46–3.53, $p < 0.001$), weight of excised gland(s) (OR = 0.70 per two-fold increase in weight, 95% CI: 0.55–0.89, $p < 0.003$), and preoperative peak PTH (OR = 0.55 per two-fold increase, 95% CI: 0.36–0.86, $p < 0.008$). These results inferred that a high preoperative peak calcium and a low peak preoperative PTH predicted failure independent of IOPTH results. When the model was assessed for its predictive value using a training and validation set, the AUC values were 0.79 (95% CI: 0.71–0.87) and 0.73 (95% CI: 0.62–0.84).

STUDY LIMITATIONS

This study is not without its limitations. The authors admit the potential bias created by loss of follow-up of the cohort that likely reflects the patient referral and practice pattern of the unit. Although the accepted definition of normocalcemia following parathyroidectomy is an adjusted serum calcium in the normal range at least 6 months after surgery, the median follow-up in this study was 18 days. Patients with operative failure were followed up for longer at 46 days. Therefore, the reported rate of failure is likely to be an underestimate of the true rate of persistent disease, and follow-up greater than 6 months may have identified further patients with recurrent disease. Persistent disease was defined only by postoperative serum calcium measurement, but PTH was not quantified postoperatively, which may have influenced the finding that preoperatively high calcium and low PTH were found to be risk factors for persistent disease.

It should also be stated that because the results are from a single tertiary endocrine unit, with a modest AUC for predictive value in an internal validation group, they may not translate into nontertiary referral center practice. The variables examined in the study did not include number of surgeons, operator experience, and annual operator volume, which are likely to play a significant role in intraoperative decision-making. However, unit-level outcomes are accepted as a valid method of reporting and reflect the available infrastructure and expertise available to the patients treated there.

Last, over a relatively long study period of 15 years, operative and laboratory protocols are likely to have changed, and therefore sensitivities of calcium and PTH assays may have changed. Indication for surgery; whether normocalcemic patients have been included (particularly as postoperative PTH levels were not measured); and use of other intraoperative adjuncts such as frozen section, indocyanine green, etc., were not reported but may have influenced outcomes. Data on whether patients were discharged on calcium supplements and their preoperative vitamin D status was also not included.

STUDY IMPACT

One of the principal strengths of this study is the large cohort of patients studied in a high-volume endocrine surgery unit with an excellent reported cure rate allied to careful statistical analysis that identified significant independent variables that predict operative failure. Over the last few decades parathyroid surgery has evolved with important modifications in preoperative and intraoperative adjuncts to enhance postoperative normocalcemia rates. Moreover, the technical approach to primary hyperparathyroidism has progressed toward targeted or focused surgery for the majority of patients. In the study period about three-quarters of patients underwent focused surgery (minimally invasive parathyroidectomy [MIP]), of which 10.6% were converted to four-gland explorations, and 25.3% had a planned four-gland exploration, demonstrating what can be achieved in a high-volume unit. The identification of perioperative patient factors that predict persistent disease should allow the operator to modify operative strategy accordingly. In the study, these were identified as a higher peak preoperative calcium level, a lower preoperative PTH level, failure to meet IOPTH criteria for cure, and lower weight of excised gland(s). Conversely, these variables showed moderate predictive value when used on an internal validation set within the study institution. The authors concluded that the presence of these findings should raise the suspicion of MGD and lower the threshold to continue monitoring IOPTH beyond the standard institutional criteria or convert to bilateral neck exploration.

RELEVANT ADDITIONAL STUDIES

The most common reasons for persistent disease after parathyroid surgery are negative neck exploration, failure to identify and resect an ectopic located gland, failure to recognize MGD, or insufficient excision of hyperfunctioning tissue.[5,9] The effect of hospital and surgeon volume of parathyroid surgery on post-parathyroidectomy outcomes is well described, with low-volume settings drifting to worse postoperative outcomes not only for cure but also for reoperation, morbidity, and cost.[10] Categorizing patients at risk of sporadic MGD is the foremost challenge for parathyroid surgeons because it permits focused surgery in the majority and reserves bilateral neck exploration for those that need it, thus ensuring a high cure rate. The study by Cron et al. suggests a high peak preoperative calcium and low peak PTH level are suggestive of MGD. Other large retrospective studies have failed to demonstrate preoperative parameters of calcium and/or PTH to be independent risk factors for operative failure/missed MGD.[8] In a multicenter study of 14,000 patients, Yeh et al. did not find a significant difference in persistent disease between patients with preoperative calcium levels separated into three groups (<11, 11.6–12.4, and >12.5 mg/dL) or PTH levels dichotomized into two groups (<100 and ≥100 pg/mL).[2] More recently, an analysis of a series of 2,000 consecutive patients undergoing bilateral neck exploration reported the converse to Cron et al., i.e., a lower calcium value, to be suggestive of MGD.[11]

Other relevant studies aiming to identify perioperative variables to predict patients at risk of MGD are listed next. Kebebew et al. studied a cohort of 238 patients and ascribed one point each for a high preoperative calcium, high preoperative intact PTH, positivity of sestamibi and ultrasound for one enlarged gland, and concordant ultrasound and

sestamibi, which were added to form a composite score, known as the CaPTHUS score.[12] A score of 3 or more had a positive predictive value of 100% for single-gland disease, thus permitting focused parathyroidectomy with no requirement for IOPTH or additional localization studies being performed. Mazeh et al. studied a cohort of 1,235 patients and developed the Wisconsin Index (WIN).[13] This was constructed by multiplying the preoperative calcium with the preoperative PTH and dividing the results into three categories (low, medium, and high scores). These groups were then combined with the excised parathyroid gland's weight intraoperatively, to form a nomogram that predicts the likelihood of additional hyperfunctioning parathyroid glands. Use of the nomogram aids decision-making to continue neck exploration or await the IOPTH outcome. The authors reported an R(2) value of 0.96 when tested in a validation cohort. Interestingly, both the CaPTHUS score and the WIN nomogram did not accurately predict single-gland disease when tested for validity in two UK endocrine units, and therefore may not be generalizable.[14]

Udelsman et al. studied 617 patients and developed an ideal theoretical mathematical model with IOPTH parameters to derive intraoperative predictability curves and found their intraoperative prediction software expedited termination of surgery with a high level of curative confidence.[15] The software accurately predicted cure in 95 patients out of 100; moreover, the software predicted residual hyperfunctioning tissue in all tested multigland patients.

Given the short duration of follow-up in the study by Cron et al., it is important to note that with longer-term follow up, patients with recurrent disease will be identified and the surgical approach used in the index operation may be a contributing factor.[16,17] With no established evidence-based guidelines for the length of follow-up of patients after parathyroid surgery, those at high risk, e.g., patients with MGD, may benefit from enhanced surveillance.

Most recently, Shirali et al. investigated early predictors of recurrent disease after initial successful parathyroid surgery.[18] Some 522 patients underwent initial successful parathyroidectomy; after a median follow-up of 30.9 months, 13 (2.5%) patients were found to have recurrent disease. On multivariate analysis age >66.5 years, calcium ≥9.8 mg/dL (2.45 mmol/L), and parathyroid hormone ≥80 pg/mL at 6 months postoperatively were associated with an increased risk of recurrence. Furthermore, the presence of at least one preoperative imaging study that conflicted with intraoperative findings among those undergoing minimally invasive parathyroidectomy was associated with increased risk of recurrence (hazard ratio 4.93, 95% confidence interval 1.25–16.53, $P = 0.016$). These parameters could be used to stratify patients who are at risk of recurrence after initial successful surgery.

To conclude, there is currently no single ideal protocol available to the parathyroid surgeon to predict operative failure following parathyroidectomy. However, the preoperative presence of low peak PTH and higher peak serum calcium, accompanied by low gland weight intraoperatively, should lower the threshold for the surgeon to undertake four-gland exploration.

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Chapter 46

MEN1: Hyperparathyroidism

Review by David Leong and Stan Sidhu

Landmark Paper

SINGLE GLAND EXCISION FOR MEN1-ASSOCIATED PRIMARY HYPERPARATHYROIDISM

Manoharan J, Albers MB, Bollmann C, Maurer E, Mintziras I, Wächter S, Bartsch DK. *Clin Endocrinol (Oxf).* 2020;92(1):63–70. doi: 10.1111/cen.14112

RESEARCH QUESTION/OBJECTIVES

To compare the long-term results of either single-gland excision (SGE one to two glands), subtotal parathyroidectomy (SPTx), or total parathyroidectomy (TPTx) for the treatment of multiple endocrine neoplasia type 1 (MEN1)–associated primary hyperparathyroidism (pHPT).

STUDY DESIGN

A retrospective study of 89 MEN1 patients from a prospectively maintained database surgically treated for pHPT between 1987 and 2017 in Germany.

SAMPLE SIZE

Eighty-nine MEN1 patients with pHPT.

INCLUSION/EXCLUSION CRITERIA

All patients had a confirmed diagnosis of MEN1 with a positive germline mutation test. Patients were excluded if they did not meet criteria for pHPT, defined as a calcium level >2.6 mmol/L and intact parathyroid hormone (PTH) >65 pg/L in the presence of a normal creatine clearance. Patients were also excluded if they did not undergo surgery for hyperparathyroidism.

INTERVENTION OR TREATMENT RECEIVED

Out of 89 patients, 38 (42.7%) had TPTx and autotransplantation with cervical thymectomy, 23 (25.8%) underwent SPTx with cervical thymectomy, and 28 (31.5%) SGE. From the 28 cases undergoing SGE, 5 had a unilateral clearance, with one including cervical thymectomy.

DOI: 10.1201/9781003196211-46

RESULTS

The main outcome of this study was to compare the long-term results of the different surgical approaches for the treatment of MEN1-associated pHPT and to evaluate durable remission and risk of hypoparathyroidism. A **biochemical cure** was defined as a calcium <2.6 mmol/L and intact PTH <65 pg/L. **Persistent disease** was defined as elevated calcium and intact PTH levels beyond 6 months postoperatively. Patients who were initially cured but developed high calcium and intact PTH levels after 6 months were classified as having **recurrent disease**. **Transient postoperative hypoparathyroidism** was defined as postoperative low serum calcium (≤2.0 mmol/L) and low intact PTH (<15 pg/L) levels. Permanent hypoparathyroidism was diagnosed if those low values persisted longer than 6 months postoperatively.

There were no differences in symptoms, mean preoperative calcium, or PTH levels between the groups. The authors reported no statistically significant differences ($p = 0.052$) in the presence of persistent disease between groups after surgery at 14.2%, 0%, and 2.6% for SGE, SPTx, and TPTx, respectively. The rate of recurrence, however, was significantly higher for SGE (21.3%) compared to SPTx (10.1% $p = 0.03$) and TPTx (4.4% $p = 0.001$). Median recurrence-free times were significantly shorter for SGE (101 months) compared to SPTx (139 months; $p = 0.018$) and TPTx (204 months; $p = 0.049$). There was no significant difference in recurrence-free time ($p = 0.35$) between the SPTx and TPTx groups. There were no reported cases of hypoparathyroidism in SGE patients, but significantly ($p = 0.01$) higher rates were found in those undergoing SPTx (17%) and TPTx (32%) (Table 46.1).

STUDY LIMITATIONS

The study is limited by its retrospective nature and relatively small patient population. Despite the authors finding no significant differences in rates of persistent HPT ($p = 0.052$), a larger cohort would likely make the difference significant. Also, despite no permanent hypoparathyroidism observed in the patients who initially had SGE, the rates of permanent hypoparathyroidism in those who had undergone a reoperation was not reported.

A further limitation is that some study patients were managed by a different institution with potentially different protocols. Finally, there appears to be a wide range of follow-up times, with a range of up to 3–301 months in patients undergoing SGE. It is possible that patients with a shorter follow-up time may have received their treatment elsewhere. It is also not clear whether length of follow-up differed between treatment groups.

Table 46.1 Summary of landmark paper outcomes

Procedure	n	Persistence	Recurrence	Recurrence Free Interval in Months (Range)	Hypoparathyroidism	Reoperation
SGE	28	4 (14.2%)	19 (21.3%)	101 (3–301)	0 (0%)	17 (60.7%)
SPTx	23	0 (0%)	9 (10.1%)	139 (28–278)	4 (17%)	4 (17%)
TPTx	38	1 (2.6%)	4 (4.4%)	204 (75–396)	3 (11%)	3 (11%)

STUDY IMPACT

This article describes the largest series of MEN1 patients undergoing SGE as an operative approach. The timing of surgery in MEN1 for pHPT is controversial, with some patients operated on at diagnosis and others only when symptoms arise or serum calcium levels exceed 1 mg/dL above the upper range of normal.[1,2] It is imperative that clinicians remember that recurrence is inevitable for most patients over their lifetime, regardless of procedure performed, and that timing is key to avoid the excessive morbidity associated with reoperation. The other significant morbidity associated with surgery for pHPT in MEN1 disease is permanent hypoparathyroidism. Long-term permanent hypoparathyroidism has documented profound effects such as increased risk of fractures, neuropsychiatric disorders, and renal dysfunction.[3,4]

Based on their study, the authors recommend consideration of SGE or a unilateral exploration, with or without thymectomy, in selected patients with localized disease on preoperative imaging with 99Tc-MIBI scintigraphy and ultrasound. They also recommended use of intraoperative PTH monitoring (ioPTH) with a 50% drop in ioPTH 15 minutes after removal of the enlarged gland to confirm adequate excision. This approach, despite a higher recurrence rate, eliminated the risk of temporary and permanent hypoparathyroidism over a median recurrence-free time of 8.9 years.

RELEVANT ADDITIONAL STUDIES

Most earlier studies published on the management of pHPT in MEN1 patients have focused primarily on a comparison between TPTx and SPTx. There have been a few studies examining less-than-subtotal parathyroidectomy (LSPTx) as an approach, which includes SGE and unilateral clearance with thymectomy. All of these studies report no cases of permanent hypoparathyroidism and a recurrence rate of up to 41%.

Versnick et al.[5] reported no recurrences or hypoparathyroidism in 12 MEN1 patients undergoing SGE over a follow-up period of 19 months. Kluijfhout et al.[6] similarly compared 8 patients with a unilateral clearance to 16 with SPTx and reported no differences in recurrence (13% vs. 31% $p = 0.54$) over 4 years and no cases of permanent hypoparathyroidism.

Montenegro et al.[7] reported a 10% rate of persistent hyperparathyroidism but no recurrences in ten patients who had undergone either a unilateral approach or LSPTx, with no cases of permanent hypoparathyroidism. Choi et al.[8] reported no significant differences ($p = 0.076$) in recurrence rates in 12 patients treated with LSPTx (25%) compared to SPTx and TPTx (50% and 5.9%, respectively) over a median follow-up period of 58 months. Lamas et al.[9] reported significantly ($p < 0.05$) higher rates of recurrence (41%) in 15 patients managed by LSPTx compared to SPTx (9%) and TPTx (25%), but no hypoparathyroidism compared to rates of 39% and 20% for SPTx and TPTx, respectively, over a median follow-up of 111 months. The results are summarized in Table 46.2.

In 2021, Nastos et al.[10] published a meta-analysis of 21 studies comparing surgical approaches to parathyroidectomy in MEN1 and demonstrated no significant differences in recurrence rates between TPTx and SPTx (relative risk [RR] 0.69 95% confidence

Table 46.2 Results of studies comparing LSPTx as the primary operative approach for primary hyperparathyroidism in MEN1 patients

Authors	*n*	Follow-up	Persistent pHPT	Recurrent pHPT	Permanent Hypoparathyroidism
Versnick et al.[5]	12 LSPTx	19 months	0% LSPTx SPTx and TPTx not reported	0% LSPTx 30% SPTx 30% TPTx $P = 0.20$	0%: LSPTx 40% SPTx 60% TPTx $P = 0.027$
Kluifjhout et al.[6]	8 LSPTx 12 SPTx	48 months	13% LSPTx 6% SPTx $P = 1.00$	13% LSPTx 31% SPTx $P = 0.54$	0% LSPTx 12.5% SPTx $P = 0.54$
Montenegro et al.[7]	10 LSPTx 22 SPTx 39 TPTx	12 months	10% LSPTx 13.6% SPTx 5.1% TPTx P = Not reported	0% LSPTx 4.5% SPTx 5.1% TPTx P = Not reported	0% LSPTx 13.6% SPTx 28.2% TPTx $P = 0.33$
Choi et al.[8]	12 LSPTx 4 SPTx 17 TPTx	58 months	0% LSPTx 0% SPTx 0% TPTx P = not significant	25% LSPTx 50% SPTx 5.9% TPTx $P = 0.076$	0% LSPTx 0% SPTx 35.3% TPTx $P = 0.031$
Lamas et al.[9]	15 LSPTx 34 SPTx 13 TPTx	111 months	41% LSPTx 9% SPTx 25% TPTx $P < 0.05$	18% LSPTx 43% SPTx 0% TPTx $P < 0.05$	0% LSPTx 39% SPTx 20% TPTx P = Not significant

interval [CI] 0.45–1.09 $P = 0.2$) but increased permanent hypoparathyroidism for TPTx (RR 1.61 95% CI 1.12–2.31 $P = 0.009$). Comparison between SPTx and LSPTx, which included SGE, showed increased recurrence rates in LSPTx (RR 1.37 95% CI 1.05–1.79 $P = 0.02$) but, as expected, a significantly lower risk of permanent hypoparathyroidism (RR 0.47 95% CI 0.29–0.75 $P = 0.002$).

Selecting patients for the LSPTx approach based on genotype could be a promising concept. A single small study of 73 patients reported by Pieterman et al. suggests that LSPTx in patients with nonsense or frameshift mutations in exon 2.9 and 10 had a statistically significant ($p = 0.016$) lower risk of recurrence.[11] Further studies, however, are required in this area.

All surgical approaches to treat hyperparathyroidism in MEN1 patients have drawbacks. Given that long-term survival in MEN1 is determined by pancreatic pathology, a conservative surgical approach to parathyroid disease is reasonable. A unilateral clearance with cervical thymectomy in selected patients with positive preoperative localization is an acceptable approach, reducing the risk of permanent hypoparathyroidism.

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CHAPTER 47

MEN2: Hyperparathyroidism

Review by Mechteld C. de Jong and Rajeev Parameswaran

Landmark Paper

MANAGEMENT OF THE PARATHYROID GLANDS DURING PREVENTIVE THYROIDECTOMY IN PATIENTS WITH MULTIPLE ENDOCRINE NEOPLASIA TYPE 2

Moley JF, Skinner M, Gillanders WE, Lairmore TC, Rowland KJ, Traugott AL, Jin LX, Wells SA. *Ann Surg.* 2015;262(4):641–646. doi: 10.1097/SLA.0000000000001464

RESEARCH QUESTION/OBJECTIVES

The *RET* oncogene was discovered to be the culprit for the multiple endocrine neoplasia type 2 (MEN2) syndromes in 1993,[1] which subsequently led to the concept of prophylactic surgical interventions for this group of patients. Since virtually all patients with MEN2 develop medullary thyroid carcinoma (MTC), prophylactic thyroidectomy is indicated.[2,3] However, the risk of developing primary hyperparathyroidism (PHPT) is much lower and ranges between 5% and 20% for all MEN2A carriers. The mean age of onset of PHPT is in the fourth decade of life, surpassing that of MTC.[4]

The management of the parathyroid glands during prophylactic thyroidectomy for MEN2A has long remained controversial, with some supporting total parathyroidectomy and autotransplantation,[5,6] while others recommend preserving all parathyroid glands in situ.[7,8] As there is limited data to support either approach, specifically in the prophylactic setting, the primary aim of the landmark study was to evaluate the parathyroid function after prophylactic thyroidectomy for MEN2A among two consecutive groups of patients undergoing different surgical approaches.

STUDY DESIGN

Retrospective cohort study, comparing parathyroid function after prophylactic thyroidectomy with or without routine central neck dissection (CND) and concurrent four-gland parathyroidectomy with autotransplantation for MEN2 between group A (historical, 1993–2000) and group B (2003–2015), who were all operated on at a single institution.

SAMPLE SIZE

Group A ($n = 50$) was composed of patients of ≤19 years of age who were consecutively identified through a genetic screening program as carriers of a *RET* mutation

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characteristic of MEN2A, and all underwent a prophylactic thyroidectomy between 1993 and 2000. Group B ($n = 102$) included both MEN2A and MEN2B carriers who were treated with prophylactic total thyroidectomy between 2003 and 2015, but in whom routine CND was not performed unless basal preoperative serum calcitonin level was >40 pg/mL.

INCLUSION/EXCLUSION CRITERIA

Group A ($n = 50$) was composed of patients of ≤19 years of age who were consecutively identified through a genetic screening program as carriers of a *RET* mutation characteristic of MEN2A, and all underwent a prophylactic thyroidectomy between 1993 and 2000. Group B ($n = 102$) included both MEN2A and MEN2B carriers who were treated with prophylactic total thyroidectomy between 2003 and 2015, but in whom routine CND was not performed unless basal preoperative serum calcitonin level was >40 pg/mL. Importantly, in this group, all viable parathyroid glands were preserved in situ, while autotransplantation of parathyroid tissue was only performed in cases of nonviable gland appearance or of an inability to preserve in situ.

INTERVENTION OR TREATMENT RECEIVED

Group A included 23 female and 27 male patients aged 3–19 years (mean age 10 years). Preoperative plasma calcitonin levels were normal in 27 and raised in 23. All patients in this group underwent a total thyroidectomy, concurrent CND, and a four-gland parathyroidectomy with autotransplantation of parathyroid fragments.

There were 44 female and 58 male patients, ranging in age from 4 months to 81 years (mean age 17.6 years) in group B, of whom there were 97 with MEN2A and 5 with MEN2B. Preoperative basal serum calcitonin levels ranged from undetectable to 6,000 pg/mL. Total thyroidectomy only was performed in 33 patients, total thyroidectomy with autotransplantation of one to four glands in 52 patients, and total thyroidectomy plus CND with autotransplantation of one to four glands in 17 patients. Specifically, for those patients with PHPT ($n = 2$) or with a strong family history of PHPT ($n = 3$), a four-gland parathyroidectomy with autotransplantation was performed.

RESULTS

In group A, the postoperative serum calcium levels were evaluated at least 1 year postoperatively and were normal in the majority ($n = 47$; 94%). However, three patients (two 4-year-olds and one 6-year-old) required supplementation of calcium and vitamin D to maintain their serum calcium levels within or near the normal range.

In group B, four patients (4%) developed postoperative hypoparathyroidism. Transient symptomatic hypocalcemia requiring administration of intravenous calcium occurred in three (two 7-year-olds and one 11-year-old). Two of these underwent total thyroidectomy

with autotransplantation of one and three parathyroid glands, respectively, while the third underwent total thyroidectomy and CND with autotransplantation of four glands. One patient (a 10-year-old) who underwent total thyroidectomy alone remained on calcium supplements for treatment of long-term hypoparathyroidism.

Comparing the two cohorts, the rates of long-term hypoparathyroidism were not statistically significantly different, at 6% for group A compared with 1% in group B ($p = 0.1062$). Importantly, at the time of last follow-up, none of the patients had developed PHPT, regardless of whether the parathyroid glands were preserved or transplanted.

STUDY LIMITATIONS

This study is a retrospective cohort study, comparing a historical cohort with one more recently treated. There are limitations inherent to the nature of this study design, such as potential missing data or uncontrolled confounding factors. Moreover, as the two compared groups were operated on sequentially, with a period of over 20 years between the first and last inclusion, other, unknown biases could have occurred. Furthermore, although the scope of this current study was to assess the difference in parathyroid outcomes, only limited data is presented regarding this subject for the historical cohort (group A). Lastly, there is limited presented data regarding the long-term outcomes concerning subsequent development of PHPT, as none of the patients developed this disease during the follow-up period. This finding may reflect the highly selected nature of the cohort of patients developing PHPT in the setting of MEN2A; however, it is notable that the length of follow-up for the group that underwent parathyroid preservation, from 2003 to 2015, was shorter than that of the historical control group that had surgery between 1993 and 2000. Given that the risk of PHPT occurs at a later age than MTC in MEN patients, this is a major limitation of this study and reduces its value in drawing conclusions regarding the long-term outcome of a more conservative approach to the parathyroid glands during prophylactic thyroidectomy for MEN.

STUDY IMPACT

The current study is of importance, as it was one of the first to address the management of the parathyroid glands during prophylactic total thyroidectomy for MEN2, and it reported a low (1%) incidence of long-term hypoparathyroidism for those patients who underwent prophylactic thyroidectomy with preservation of the parathyroid glands in situ without increasing the occurrence of PHPT. This is an important finding, as thyroidectomy and parathyroidectomy in children are known to be associated with a high risk of long-term hypoparathyroidism.[9,10] Children and adolescents with long-term hypoparathyroidism are at increased risk for secondary complications, such as renal stones and decreased estimated glomerular filtration rate (eGFR).[11] Moreover, hypoparathyroidism is associated with a decreased overall quality of life.[12]

While the combined procedure of a total parathyroidectomy with autotransplantation of parathyroid fragments was used frequently prior to this landmark paper, its associated

risk of long-term hypoparathyroidism has led to a shift away from this approach, with preservation of the parathyroid glands in situ now becoming paramount. Overall, this study contributed toward a paradigm shift, focusing more on reducing surgical morbidity and improving the quality of life in MEN2A patients, with parathyroid preservation at prophylactic thyroidectomy followed by biochemical surveillance and targeted parathyroid surgery subsequently if needed.

RELEVANT ADDITIONAL STUDIES

The consequences of developing hypoparathyroidism, especially among children, has emphasized the need for a less aggressive surgical approach toward the parathyroid glands in MEN2. If PHPT develops in MEN2A patients, its nature is often mild and asymptomatic.[13] Furthermore, surgical treatment criteria are the same as for sporadic disease, as targeted removal of only the affected glands is associated with good outcomes.[8] In line with this consideration, it is not currently recommended to perform systematic prophylactic parathyroidectomy in patients with MEN2A undergoing thyroid surgery when calcium and parathyroid hormone (PTH) levels are normal.[14]

To exclude mild or asymptomatic PHPT at the time of (prophylactic) thyroidectomy, all patients should undergo appropriate screening,[15] and if PHPT is detected, management should be aimed at cure while preserving an optimal quality of life. The American Thyroid Association (ATA) guidelines provide a general recommendation for the management of PHPT, stating that only visibly enlarged parathyroid glands should be resected. Moreover, for those patients who develop PHPT subsequently to their thyroidectomy, localization studies should be employed prior to repeat surgery.[15]

For most MEN2 patients, PHPT will only develop after prophylactic thyroidectomy or onset of MTC; thus, screening is recommended. It has been shown that a mutation in codon 634 is associated with a moderate penetrance of PHPT (up to 30%), while mutations in codons 609, 611, 618, and 620 are associated with a much lower penetrance, ranging between 2% and 12%.[15,16] Therefore, the ATA guidelines propose annual screening start at 11 years of age for those with codon 634 mutations and at 16 years of age for mutations in the remaining codons.[15,17]

Conversely to this screening advice, the recommended extent of parathyroid resection for PHPT is not currently guided by the codon in which the mutation is found. Based on the relatively higher incidence of hyperplastic parathyroid glands among those with a high-risk mutation (versus one or more parathyroid adenomas), a more tailored resection could be considered. The proposed algorithm illustrates a codon-directed management of PHPT among MEN2 carriers (Figure 47.1). This codon-tailored approach does not alter the initial surgical approach during (prophylactic) thyroidectomy for those without a concurrent PHPT diagnosis, as non-affected parathyroid glands would be preserved in situ. Even though this phenotype/genotype correlation is well established at a population level, there is a range of disease prevalence among individual MEN2A families, suggesting additional influences of yet unknown modifying or environmental factors.[18,19]

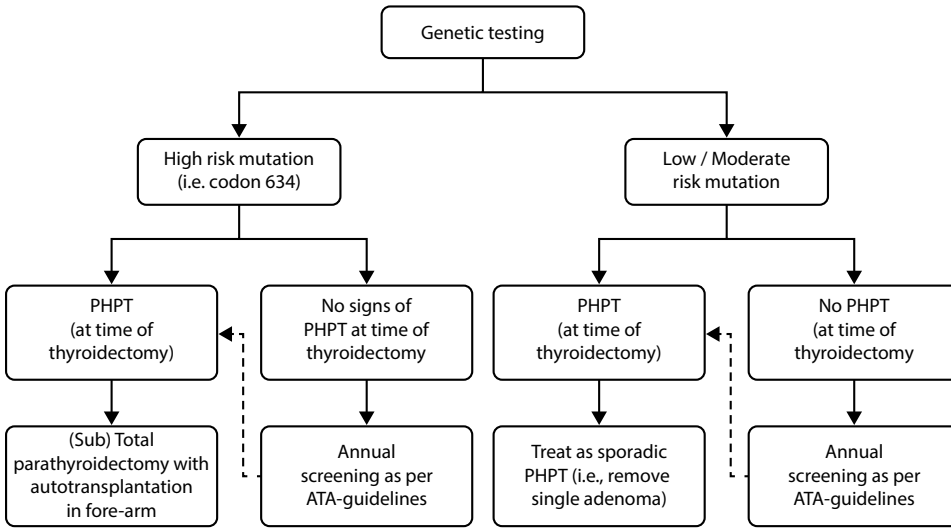

Figure 47.1 An algorithm to provide guidance toward codon-directed therapy for PHPT among carriers of MEN2 mutations.

Due to its relative rarity, the precise epidemiology of PHPT among those with MEN2A remains to be further elucidated. Future studies should be aimed at carrying out an even more detailed assessment of the genotype/phenotype association, as well as other modifying factors, to potentially even further individualize the surgical management of the parathyroid glands in MEN2A patients.

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CHAPTER 48

Secondary Hyperparathyroidism

Review by Hadiza S. Kazaure and Julie Ann Sosa

Landmark Paper

RECENT CHANGES IN THERAPEUTIC APPROACHES AND ASSOCIATION WITH OUTCOMES AMONG PATIENTS WITH SECONDARY HYPERPARATHYROIDISM ON CHRONIC HEMODIALYSIS: THE DOPPS STUDY

Tentori F, Wang M, Bieber BA, Karaboyas A, Li Y, Jacobson SF, Andreucci VE, Fukagawa M, Frimat L, Mendelssohn DC, Port FK, Pisoni RL, Robinson BM. *Clin J Am Soc Nephrol.* 2015;10(1):98–109. doi: 10.2215/CJN.12941213

RESEARCH QUESTION/OBJECTIVES

Secondary hyperparathyroidism (SHPT) is associated with high-turnover bone disease, fractures, cardiovascular events, and mortality among patients with end-stage renal disease (ESRD).[1–4] SHPT is characterized by an increase in parathyroid hormone (PTH) secondary to parathyroid hyperplasia. PTH can be regulated via medical management or parathyroidectomy. Advances in pharmacologic therapy, including the introduction of active vitamin D analogs and cinacalcet, both of which lower PTH levels, have influenced practice guidelines aimed at improving the outcomes of ESRD patients with SHPT. Although there have been no randomized controlled trials comparing surgical versus medical management of SHPT, and none determining whether treatment to a specific PTH target improves outcomes, several studies have shown that a high PTH level is associated with all-cause mortality and that parathyroidectomy is associated with improved outcomes and lower mortality.[4–12] However, there is considerable uncertainty around the optimal PTH threshold that should prompt parathyroidectomy. In this selected landmark study, Tentori et al.[13] aimed to answer two pertinent questions:

- Have patterns of care for ESRD patients with SHPT changed over time?
- What is the association between PTH level and clinical outcomes (mortality and hospitalization) among patients with SHPT?

STUDY DESIGN

Data were derived from the international Dialysis Outcomes and Practice Patterns Study (DOPPS) and were collected prospectively in three geographic regions categorized as Europe-Australia-New Zealand (Eur-A/NZ), Japan, and North America. Trends in PTH levels, SHPT interventions (medical and surgical), and outcomes were examined

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across five study phases (phase 1: 1996–2001; phase 2: 2002–2004; phase 3: 2005–2008; phase 4: 2009–2011; phase 5: 2012–2015). In each phase, a new random sample of hemodialysis facilities was selected from which 20–40 patients were selected randomly for inclusion in the study.

SAMPLE SIZE

There were a total of 43,819 patients in the study population. Due to limited follow-up outcome data for phase 5 patients, analysis of the association between PTH and outcomes was restricted to 35,655 patients.

INCLUSION/EXCLUSION CRITERIA

The study included participants who had been on hemodialysis for at least 90 days, had at least one PTH value, and had no history of having undergone parathyroidectomy. Patients <18 years of age were excluded.

INTERVENTION OR TREATMENT RECEIVED

There were three intervention groups: 1) medical management (active vitamin D analogs and/or cinacalcet) only, 2) parathyroidectomy, and 3) no treatment.

RESULTS

Trends in Practice Patterns

Tentori and colleagues found that the use of vitamin D analogs and cinacalcet increased over time in all study regions ($p < 0.001$). In contrast, parathyroidectomy rates decreased significantly in all regions ($p < 0.001$). This trend was particularly evident after the introduction of cinacalcet in phase 3; peak parathyroidectomy rates occurred in phase 2, decreasing from approximately 17% to 8% in the Eur-A/NZ region, from 12% to 3% in Japan, and from 12% to 8% in North America.

Association of PTH with Outcomes

PTH Trend over Time

There was relative stability in serum calcium and phosphorus levels despite the changes in management patterns described earlier. However, median PTH levels increased substantially in all regions except Japan. This correlated with a higher *target* PTH level as reported by dialysis unit medical directors surveyed in the study: The median PTH target increased from 233 pg/mL to 450 pg/mL in the Europe-A/NZ study region and from 250 pg/mL to 500 pg/mL in North America. In particular, the proportion of ESRD patients with a PTH level >600 pg/mL increased 6.3-fold, from 3.3% to 24.1% in Europe-A-NZ and 15.5-fold (from 2.6% to 42.9%) in North America. Overall, patients with a PTH >600 pg/mL constituted 11% of the study sample, and they were more likely to be black, younger, and have fewer comorbidities.

Association of PTH with Adverse Clinical Outcomes

The overall all-cause and cardiovascular mortality rates were 22.8% and 8.7%, respectively; 53.8% of patients experienced ≥1 all-cause hospitalization, and 23.2% had a cardiovascular-related hospitalization in the median 1.61 years of follow-up time. Only 6% of patients underwent a kidney transplant during the entire study period.

Compared with the reference group (PTH 150–300 pg/mL), adjusted all-cause mortality was higher for patients with a PTH 301–450 pg/mL (hazard ratio [HR], 1.09; 95% confidence interval [95% CI)], 1.01–1.18; $p = 0.02$) and >600 pg/mL (HR, 1.23; 95% CI, 1.12–1.34; $p < 0.001$). These results were consistent in several sensitivity analyses. In an analysis using median PTH values during baseline time intervals as the predictor, patients with a median PTH >600 pg/mL had higher mortality compared with the 150–300 pg/mL group (median PTH at 1–3 months: HR, 1.20; 95% CI, 1.09–1.32; 1–6 months: HR, 1.14; 95% CI, 1.03–1.27; 1–12 months: HR, 1.21; 95% CI, 1.06–1.37). In instrumental variable analyses wherein PTH levels were dichotomized at different cutoff points, higher mortality was again observed for PTH >600 pg/mL (vs. ≤600 pg/mL), with a hazard ratio of 1.62 (95% CI: 1.12–2.35, $p = 0.02$); the association remained positive but was somewhat weaker at lower PTH cutoff points.

To assess the association between PTH and outcomes independent of the potential effect of SHPT treatments, the authors conducted a sub-analysis of untreated patients (those not receiving vitamin D analogs or undergoing parathyroidectomy). They found that a PTH <50 pg/mL was significantly associated with mortality (HR, 1.25; 95% CI, 1.04–1.51) and that the mortality risk associated with a PTH >600 pg/mL trended toward statistical significance (HR, 1.15; 95% CI, 0.86–1.53, $p > 0.05$). However, the number of untreated patients was small ($n = 350$), limiting statistical power.

STUDY LIMITATIONS

Noteworthy limitations of the study include PTH assay variability which restricts direct comparison across DOPPS centers and study phases. Causality between a high PTH (>600 pg/mL) and mortality cannot be deduced due to the nonrandomized study design. Long-term follow-up data is also limited. Further, the reasons why medical directors at DOPPS participating centers favored a high PTH target over time are unknown. Unfortunately, the study does not provide insight into why parathyroidectomy rates decreased in almost all regions over time. For patients who underwent parathyroidectomy, trends and differences in operative approach were not examined.

STUDY IMPACT

In their use of a large dataset and refined statistical methodology, Tentori et al.'s landmark study revealed several important findings, including 1) evidence of preferential utilization of medical management over parathyroidectomy worldwide; 2) dramatic liberalization of PTH targets that predate the liberalization of PTH targets in practice guidelines; 3) demonstration of a U-shaped association between PTH and mortality, with mortality risk increased when PTH is <50 pg/mL or ≥300 pg/mL, and especially

when PTH is >600 pg/mL; and 4) suggestion of care disparities among SHPT patients. Considering that patients who have a PTH >600 pg/mL were generally younger and had fewer comorbidities, the study uncovered an interesting paradox – that parathyroidectomy rates were decreasing parallel to an increase in the subpopulation of patients who had a PTH >600 pg/mL *and* had baseline characteristics that potentially render them at lower risk of surgical complications.

RELEVANT ADDITIONAL STUDIES

Tentori et al.'s landmark paper was published approximately 12 years after the initial 2003 Kidney Disease: Improving Global Outcomes (KDIGO) practice guidelines included a recommendation that a medically refractory PTH ≥800 pg/mL should be considered an indication for parathyroidectomy.[14] Six years later, the revised guidelines[15] eliminated this recommendation and liberalized the PTH target from 150–300 pg/mL to a target PTH that is "2-9 times the upper range of normal." This PTH target corresponds to a PTH target of 130–600 pg/mL in various PTH assays. Spanning the period wherein KDIGO guidelines are formulated and revised, Tentori et al.'s study therefore revealed growing apathy toward parathyroidectomy at a time of considerable uncertainty on optimal PTH targets for SHPT patients.[16–18] This uncertainty persists, as demonstrated by the unchanged recommendations in the most recent KDIGO guidelines.[19]

Are nephrologists increasingly less likely to refer patients for parathyroidectomy? Are surgeons more reluctant to operate on SHPT patients? Or are SHPT patients increasingly disinclined to undergo parathyroidectomy? The reasons why parathyroidectomy rates have decreased worldwide remain understudied.[20–22] There is also a scarcity of data on the perceptions of physicians (surgeons and nonsurgeons) on what constitutes acceptable criteria for parathyroidectomy referral and acceptable postoperative risks for ESRD patients.[20] Using data from the U.S. Renal Data System, Ishani et al.[23] examined the outcomes of 4,435 SHPT patients who underwent parathyroidectomy; 30-day readmission and mortality rates were 23.8% and 2%, respectively. Commenting on Ishani et al.'s and Tentori et al.'s studies (published in the same *CJASN* journal edition), one reflective piece described Ishani et al.'s findings as "harrowing," indicating the general concern nephrologists have for the safety of parathyroidectomy among ESRD patients.[24]

The tide against parathyroidectomy may turn soon, even as debates continue around criteria for surgical candidacy[25,26] and the optimal operative approach for managing SHPT.[27,28] Recently, Komaba et al.'s prospective study[29] – the closest to a randomized study there has been to date – showed a 22% survival benefit for patients with a PTH ≥ 300 pg/mL who underwent parathyroidectomy as compared to propensity-matched patients who were managed medically. The survival benefit was more pronounced among patients with PTH ≥500 pg/mL. Other comparative studies have reported up to an 86% reduction in cardiovascular mortality as well as improved quality of life for SHPT patients undergoing parathyroidectomy versus those treated medically.[30,31] More methodologically robust studies are certainly needed, but one crucial reality ultimately stands out – there exists an incredible paucity of interdisciplinary, collaborative research by surgeons and nephrologists aimed at improving the care of ESRD patients with SHPT.

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Chapter 49

Tertiary Hyperparathyroidism

Review by Thomas Burton and Goswin Meyer-Rochow

Landmark Paper

A RANDOMIZED STUDY COMPARING PARATHYROIDECTOMY WITH CINACALCET FOR TREATING HYPERCALCEMIA IN KIDNEY ALLOGRAFT RECIPIENTS WITH HYPERPARATHYROIDISM

Cruzado JM, Moreno P, Torregrosa JV, Taco O, Mast R, Gómez-Vaquero C, Polo C, Revuelta I, Francos J, Torras J, García-Barrasa A, Bestard O, Grinyó JM. *J Am Soc Nephrol.* 2016;27(8):2487–2494. doi: 10.1681/ASN.2015060622

RESEARCH QUESTION/OBJECTIVES

Secondary hyperparathyroidism (SHPT) is a common complication of end-stage renal failure (ESRF) resulting from continuous stimulation of parathyroid tissue to maintain calcium and phosphate homeostasis. Following renal transplantation, persistent or tertiary hyperparathyroidism (THPT) can be present in 17–50% of recipients due to the loss of parathyroid hormone (PTH) calcium-dependent autoregulation.[1–4]

Despite advances in transplant care and immunosuppressive therapy, renal transplant patients with persistent hyperparathyroidism often have worse long-term outcomes with chronic allograft damage and cardiovascular complications due to the resulting hypercalcaemia.[5] Subtotal parathyroidectomy (SPT) has traditionally been the main therapeutic treatment option for THPT due to the risk of medical therapy with vitamin D supplementation or vitamin D analogues potentially resulting in worsening of hypercalcemia, although surgery is not without risk of complications.[6,7] The development of calcimimetic medications has allowed for the emergence of a pharmacological treatment option for hypercalcemia caused by hyperparathyroidism without exposing patients to the risks of surgery.[8,9] Calcimimetic agents enhance the sensitivity of calcium-sensing receptors (CaRs) on the parathyroid glands, thereby suppressing PTH production and resulting in reduced serum calcium levels.[10] The primary aim of this landmark study was to evaluate whether SPT is more effective than the calcimimetic agent cinacalcet for the management of hypercalcemia caused by THPT after kidney transplantation.

STUDY DESIGN

A 12-month prospective, multicenter, open-label, randomized control trial was undertaken in Spain between January 2010 and September 2014 comparing the outcomes of patients with persistent hyperparathyroidism and hypercalcemia after renal transplantation treated by cinacalcet or SPT.

DOI: 10.1201/9781003196211-49

SAMPLE SIZE

A total of 30 patients who met the inclusion criteria were randomized evenly (1:1) between cinacalcet ($n = 15$) or subtotal parathyroidectomy ($n = 15$).

INCLUSION/EXCLUSION CRITERIA

Inclusion criteria for patients were defined as at least 6 months post kidney transplant with a functioning renal allograft (estimated glomerular filtration rate [eGFR] ≥30 mL/min) and biochemical evidence of persistent hyperparathyroidism (serum intact parathyroid hormone [iPTH] ≥15 pmol/L, corrected total serum calcium ≥2.63 mmol/L and serum phosphate ≤1.2 mmol/L). Patients were excluded if these criteria was not met or cinacalcet therapy or surgery was contraindicated.

INTERVENTION OR TREATMENT RECEIVED

Patients assigned to cinacalcet initially received 30 mg/day which was subsequently titrated to achieve normocalcemia. Patients randomized to SPT underwent surgery by an experienced parathyroid surgeon in a tertiary care hospital. Bilateral parathyroidectomy was performed with a remnant equivalent to one normal gland in size (50 mg) left in situ. Transcervical thymectomy was performed to ensure removal of any potential ectopic parathyroid tissue located within the thymus. Intraoperative PTH was measured at baseline and 10 minutes after resection to confirm an adequate biochemical response to surgery. Both intervention groups had baseline assessment and were followed up at 3, 6, and 12 months.

RESULTS

The primary end point of achieving normocalcemia (serum calcium 2.22–2.55 mmol/L) at 12 months postoperatively was achieved in all 15 patients who underwent SPT compared to 10 patients (67%) in the cinacalcet group ($p = 0.04$) (Figure 49.1).

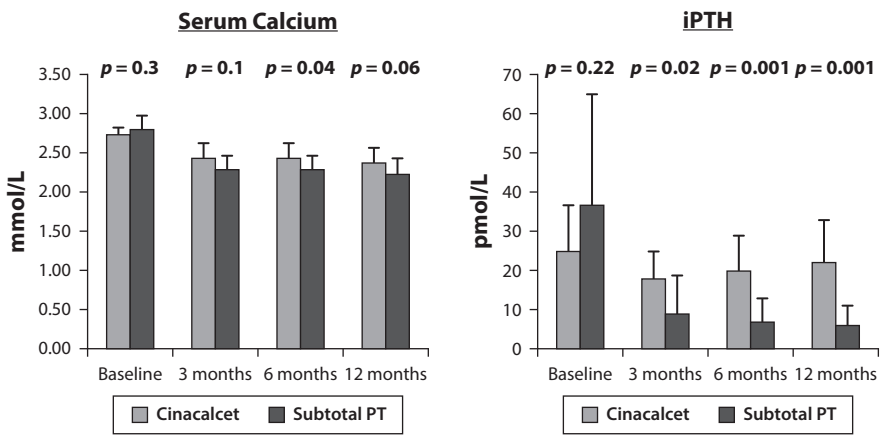

Figure 49.1 Evolution over time of serum calcium and iPTH levels in the cinacalcet and subtotal parathyroid groups. (Adapted from Cruzado et al., 2016.)

Table 49.1 Serum measurements over time of key end points

	Cinacalcet			Subtotal Parathyroidectomy		
Variable	Baseline	6 Months	12 Months	Baseline	6 Months	12 Months
Calcium, mmol/L	2.72 ± 0.1	2.42 +/- 0.2[a]	2.37 ± 0.2[a]	2.78 ± 0.2	2.26 ± 0.2[b*]	2.22 ± 0.2[b*]
Albumin, g/L	43.9 ± 2.8	43.9 ± 2.5	43.7 ± 3.1	44.5 ± 2.4	44.1 ± 3.3	43.4 ± 3.0
iPTH, pmol/L	25 ± 12	20 ± 9[a]	22 ± 11	37 ± 18	7 ± 6[b*]	6 ± 5[b*]
Phosphorus, mmol/L	0.92 ± 0.2	1.0 ± 0.2[a]	1.1 ± 0.1[a]	0.93 ± 0.2	1.3 ± 0.2[b*]	1.3 ± 0.3[b*]
$25(OH)D_3$, nmol/L	51 ± 24	59 ± 21	53 ± 15	41 ± 14	79 ± 31[b]	70 ± 30[b]
Renal function, eGFR mL/min	57 ± 11	53 ± 6	48 ± 14[a]	57 ± 16	53 ± 17	53 ± 14
Vascular Calcification Score	17.0 ± 13.5	18.6 ± 13.8	18.8 ± 14.2	17.7 ± 12.7	17.3 ± 13.7	17.6 ± 13.7

Source: Adapted from Cruzado et al. (2016).

[a] *p*-value <0.05 compared with baseline in cinacalcet group.
[b] *p*-value <0.05 compared with baseline in subtotal parathyroidectomy group.
[*] Denotes *p*-value <0.05 compared with cinacalcet.

Secondary end points demonstrated a statistically significant reduction of PTH levels in the SPT group compared with the cinacalcet group (10/15 vs. 0/15, $P = 0.002$) and a significant improvement in bone mineral density (BMD) in the femoral neck (0.846 g/cm^2 vs. 0.700 g/cm^2, $p = 0.01$). Although some improvement of bone density at the lumbar spine and distal radius occurred in the SPT group, this was not statistically significant. Additional secondary end points, including serum phosphate level normalization, eGFR loss, and extent of vascular calcification, did not demonstrate statistically significant differences between the two groups (Table 49.1).

Complications in both treatment arms were recorded. In the cinacalcet group, one patient discontinued treatment due to gastrointestinal intolerance and severe xerostomia and one patient required admission to hospital for severe diarrhea. Other complications involved digestive intolerance, edema, or renal dysfunction. In the SPT group, four patients developed hypocalcemia with two requiring hospitalization. Other adverse events likely related to surgical treatment included two patients with transient dysphonia and three with diarrhea.

This landmark paper also analyzed the economic cost for both treatments. The overall cost of surgical intervention (including preoperative workup) was €3,712 compared with 1 year's cost of cinacalcet at €3,003. With surgery as a one-off expense, the ongoing cost of cinacalcet after 14 months of therapy resulted in surgical intervention being the more cost-effective, long-term treatment option.

STUDY LIMITATIONS

The main limitation of this study is the short duration of follow-up, which precluded the ability to assess any potential longer-term complications associated with SPT or treatment with cinacalcet. Evaluation of renal function, renal allograft survival, bone densitometry, fracture risk, cardiovascular and ectopic calcium deposition, recurrence of hyperparathyroidism, and any difference in length of survival is likely to take longer

than 12 months to become evident. Another limitation of this article is the relatively small numbers ($n = 30$). Despite SPT for THPT being a relatively uncommon operation overall, this small number of patients may prevent assessment of true differences between treatment arms. A further criticism of this article is that the cinacalcet dosage was adjusted during follow-up visits to achieve normocalcemia without any reference to PTH levels per se. The use of a single surgeon for all subtotal parathyroidectomies ensured consistency of treatment for all patients undergoing surgery in this study; however, it does potentially limit the generalizability of the study findings.

STUDY IMPACT

The optimal management of refractory hyperparathyroidism following renal transplant is unclear due to the paucity of quality data for evidence-based treatment. This trial is the only published prospective randomized controlled trial directly comparing SPT with cinacalcet for THPT treatment. This trial demonstrates that while both medical and surgical therapy can be considered for control of hypercalcemia associated with THPT, surgical treatment is associated with higher cure rates with acceptably low complication rates, particularly when the adverse effects associated with cinacalcet treatment are also considered. Furthermore, in patients without contraindications to surgery, SPT is a more cost-effective, longer-term treatment option.

Although this study suggests superiority of SPT to cinacalcet for treatment of THPT in renal transplant patients at 12 months of follow-up, further research is required to establish the superiority of surgical management in the longer term.[5]

RELEVANT ADDITIONAL STUDIES

One difficulty in comparing this trial to other available literature is that there is no uniform definition regarding the diagnosis of THPT. Most definitions include serum PTH levels (more than two times the upper limit of normal) and persistent hypercalcemia and elevated PTH following renal transplantation.[5] Several observational and retrospective trials have been undertaken looking at the outcomes of both medical and surgical management of THPT; however, a limited number of other trials have directly compared the outcomes of these treatment options.[3,10] The effectiveness of cinacalcet against placebo in treating patients with THPT has been shown in numerous studies.[11–13] These have all demonstrated the relative effectiveness of achieving normocalcemia with relatively good safety profiles, although they have not compared the outcomes or cost-effectiveness to SPT.

The preoperative use of cinacalcet does not appear to influence the outcome for patients undergoing SPT. Mogl et al. demonstrated that while preoperative treatment with cinacalcet reduced preoperative calcium levels, this had no effect on postoperative PTH or calcium levels compared with patients not taking calcimimetic agents prior to surgery.[14]

Lou et al. retrospectively evaluated 618 renal transplant patients and found that SPT appears to be underutilized in THPT patients.[15] Over an 8-year period only 41 (6.6%)

THPT patients underwent surgery. These patients were often more symptomatic with higher PTH and preoperative calcium levels than those treated conservatively. Those individuals undergoing surgical management had serum calcium and PTH levels closer to the normal range than those undergoing medical intervention.

The safety and efficacy of SPT or total parathyroidectomy (TPT) have been demonstrated by multiple reports.[16–19] Van Der Plas et al. in 2018[16] reported low complication rates in frail patients with end-stage kidney disease. Of 187 patients undergoing surgery, there was no mortality within 30 days of the procedure, and it had relatively low complication rates (7.9%). Thirteen (7%) patients who underwent SPT or TPT required further surgery for persistent or recurrent disease in the 25-year experience of the data collection.

Ishani et al. reported a 2% inpatient and 30-day mortality rate in 4,435 dialysis-dependent patients undergoing parathyroidectomy.[19] Although a relatively high mortality figure, these patients are often much more frail and comorbid compared to those undergoing parathyroidectomy for primary or secondary HPT.

A systematic review by Tang et al. in 2017 also demonstrated the effectiveness and safety of SPT in the treatment of THPT.[20] All of the 30 studies that were included found that parathyroidectomy was an effective treatment for THPT.

Jung et al. published a retrospective analysis of 83 THPT patients who underwent kidney transplantation at a single tertiary care center in Korea.[9] At 1 year following intervention, the 64 patients treated with parathyroidectomy had lower mean serum calcium levels compared to the patients on cinacalcet (9.7 ± 0.7 mg/dL vs. 10.5 ± 0.7 mg/dL, $p = 0.001$). Notably serum PTH levels were significantly lower in the parathyroidectomy group at both 6 months (129.1 ± 80.3 pg/mL vs. 219.2 ± 92.5 pg/mL, $p = 0.002$) and 1 year (118.8 ± 75.5 pg/mL vs. 250.6 ± 94.5 pg/mL, $p < 0.001$) postoperatively. No differences in allograft outcomes, cardiovascular events, or bone density/fracture risk were demonstrated between the two groups. Dufler et al. also conducted a retrospective analysis of 94 THPT patients who underwent SPT compared to cinacalcet therapy at two academic centers in the Netherlands.[3] Both treatment arms had normalized serum calcium at 1 year; however, serum PTH remained persistently elevated in the cinacalcet group (22 pmol/L vs. 3.7 pmol/L). While the implications of this persistent elevation in PTH is not known, these results imply that surgical management leads to better disease control.

A systematic review by Dufler et al. in 2017 used data from 47 trials that assessed 1,372 patients to demonstrate higher cure rates with surgical treatment than with medical therapy for THPT.[8] While not able to directly compare outcomes within the trials, studies were included for each treatment modality to demonstrate the effectiveness of each, and then overall results were compared between surgery and cinacalcet. Thirteen trials were included that evaluated SPT and TPT with or without autotransplantation. In 158 patients undergoing SPT, 2 (1.3%) had persistent THPT and 12 (7.6%) had recurrent disease during mean follow-up (41–79 months). No patients who underwent TPT (71) had persistent disease, while only 3 (4%) developed recurrent symptoms. To further emphasize the importance of adequate experience of surgeons, 10 (91%) of 11 patients

who underwent limited parathyroidectomy (fewer than four glands identified, or one or two glands removed deliberately) had recurrent or persistent disease. Twenty-four trials were included in the cinacalcet analysis and found that 37/578 patients (6.4%) discontinued cinacalcet due to persisting hypercalcemia or side effects.

Overall, the observational trials, the selected single landmark randomized controlled trial, and a systematic review demonstrate superiority for surgical intervention compared with cinacalcet for THPT treatment. However, further larger randomized trials are required to confirm these observations and explore the long-term outcomes for both treatment options.

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Chapter 50

Classification of Parathyroid Cancer

Review by Gaurav Agarwal and Dileep Ramesh Hoysal

Landmark Paper

CLASSIFICATION OF PARATHYROID CANCER

Schulte KM, Gill AJ, Barczynski M, Karakas E, Miyauchi A, Knoefel WT, Lombardi CP, Talat N, Diaz-Cano S, Grant CS. *Ann Surg Oncol.* 2012;19(8):2620–2628. doi: 10.1245/s10434-012-2306-6

RESEARCH QUESTION/OBJECTIVES

Parathyroid carcinoma (PaCa) is a rare (0.7–2.1%) cause of primary hyperparathyroidism (PHPT), but an important cause of death in this patient population.[1–4] Its relative prevalence is higher in studies reporting predominantly symptomatic PHPT patients.[5,6] The majority of PaCa cases are sporadic and difficult to distinguish from the more common parathyroid adenomas.[5–7] Even with recent advances establishing a role for CDC73 gene mutations and resultant loss of parafibromin immunostaining in the diagnosis of PaCa, most patients are not diagnosed or staged preoperatively. A systematic radical oncologic surgical approach is reasonably well established, though not universally applied, in the absence of a preoperative diagnosis. There is also no consensus on a clinical and pathological staging system for PaCa. This landmark study aimed to validate two predefined pathological classification systems for PaCa in an independent validation cohort.

STUDY DESIGN

This was a retrospective validation study on patients recruited from the eight participating centers, based on questionnaire-based information collected from eight institutions: Mayo Clinic, Rochester, MI; Royal North Shore Hospital, Sydney, Australia; King's College Hospital, London, UK; Jagiellonian University, Krakow, Poland; University of Marburg, Marburg, Germany; Kuma Hospital, Kobe, Japan; University of Düsseldorf, Düsseldorf, Germany; and Universita Cattolica Del Sacro Cuore, Rome, Italy.

SAMPLE SIZE

Included 222 PaCa patients: 140 in the reference cohort and 82 in the validation cohort.

INCLUSION/EXCLUSION CRITERIA

Minimal study inclusion criteria required an unambiguous histopathological diagnosis of PaCa as per World Health Organization 2004 criteria: The presence of an infiltrative growth pattern with capsular invasion and with soft tissue invasion. In their absence,

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histological proof of vascular invasion (major criteria) with or without invasion of vital structures (trachea, esophagus, major vessel)[8]; additionally, the presence of locoregional or distant metastasis, a complete dataset, known margin status, and minimum 2 months follow-up were required. Patients not meeting the inclusion criteria were excluded.

INTERVENTION OR TREATMENT RECEIVED

The 140-patient "reference cohort" was obtained from the study by Talat and Schulte.[1] The validation cohort consisted of 82 PaCa patients recruited from the eight participating centers. Patient characteristics – sex; capsular, soft tissue, and vascular invasion; invasion of vital structures; lymph node metastases; and margin status of the reference cohort – were analyzed using multinominal regression, based upon which two classification schemes were derived. The classification scheme analogous to the framework of tumor, node, metastasis (TNM) staging system similar to the approach of the Union for International Cancer Control, was termed the "differentiated classification" and classified patients into "classes" I–IV. (T1 capsular invasion, T2 invading surrounding soft tissues, T3 vascular invasion, and T4 invading vital organs; N0/1 no regional/regional node metastasis and M0/1 no distant / distant metastasis; Class I T1 or T2N0M0, Class II T3N0M0, Class III Any T, N1, M0 or T4 and Class IV Any T, Any N, M1). The second simpler classification scheme, referred to as the "high-risk/low-risk classification," stratified patients into only two categories: low-risk capsular and surrounding soft tissue invasion and high-risk vascular invasion +/- lymph node metastasis +/- invasion of vital organs +/- distant metastasis. All patients in the reference and validation cohorts were stratified according to both derived classification schemes, and outcome differences between classes were reported.

Surgical interventions were categorized as being local excision only (pericapsular excision of parathyroid lesion), or en-bloc excision (oncological resection of parathyroid lesion with circumferential soft tissue as a minimal criterion with any additional surgery, e.g., ipsilateral thyroid lobectomy, central compartment lymphadenectomy, or further locoregional excision). Adverse outcome events were defined as death or disease recurrence. The primary study end point was death due to disease, assessed as risk ratio, odds ratio, and overall survival (OS) calculated by Kaplan-Meier analysis. Secondary study end points were local or distant recurrent disease identified during follow-up, assessed as risk ratio, odds ratio, and disease-free survival (DFS) calculated by Kaplan-Meier analysis. The tertiary study end point was model quality of high-risk versus low-risk classification, assessed by receiver-operating characteristic (ROC) and basic probability statistics.

RESULTS

Demographic features, macroscopic findings, and biochemical parameters did not differ significantly between validation and reference groups. Histopathological characteristics – vascular invasion, soft tissue invasion, and vital structure invasion – differed significantly between the groups. The two study cohorts had undergone similar treatment, with similar proportions undergoing oncologic resections, and had similar local and total recurrence rates. However, distant metastases were more common in the reference group, related to a higher rate of vascular invasion. Margin status was available for the validation cohort only.

High-risk patients had almost exclusively higher relative risk (RR) of death due to disease. The RR of recurrence was 12.8 times higher in high-risk patients ($p < 0.0001$). Overall DFS ($\chi 2 = 15.4$; 95% confidence interval [CI; 2.7–29.1]; $p < 0.0001$) and 5-year DFS were significantly worse in patients classified as high-risk (93.3% vs 46.7%; $\chi 2 = 8.7$, $p < 0.003$). The RR of death was infinitely higher for class II and class III compared to class I ($p < 0.0001$). There was no difference in RR of death when comparing class II with class III. Kaplan-Meier analysis confirmed the class-related progression of mortality and recurrence, with higher DFS in class I compared to classes II and III.

The area under the ROC curve (AUC) was determined for both models, showing good performance in ROC analysis. The AUC of the high-risk versus low-risk models was 0.74 for the entire cohort, 0.82 for the group undergoing local excision only, and 0.74 for the en-bloc resection group. The AUC of the differentiated classification was 0.83 for the entire cohort, 0.91 for the group undergoing local excision, and 0.79 for the en-bloc resection group. This makes it unlikely that the choice of surgical procedure had an impact on the model construction.

Patient follow-up ranged from 2 to 347 months (median 50 months, mean 76.3 ± 74 months). Eleven patients died after a median 37 months follow-up (range 9–90 months, mean 46 ± 27 months). Eighteen patients had locoregional recurrence after median 10 months follow-up (range 2–192 months, mean 32 ± 47 months), of which nine recurred within <12 months. Distant metastases were found in 11 patients after a median 48 months follow-up (range 2–300 months, mean 74 ± 75 months). In all, 38 patients died or recurred after a median 36 months follow-up (range 5–312 months, mean 75 ± 89 months). Margin status did not affect the validity of outcome prediction of high-risk versus low-risk classification systems. Kaplan-Meier analysis found significant differences across classes in the entire cohort, exhibiting significantly worse prognosis with advanced disease. Vascular invasion was uniquely associated in all patients with distant metastasis.

STUDY LIMITATIONS

Limitations include the retrospective study design and small study cohorts, though these are understandable given the rarity of PaCa. The study follow-up period was also rather short (minimum 2 months). Neither of the two predefined staging systems this study attempted to validate addressed the impact of genetic or molecular factors. Margin status did not have a role in staging the disease in this study, yet it remains an important prognostic factor and could have been compared between the two groups.

STUDY IMPACT

This study proposes a PaCa risk stratification system and a staging system, with the aim of recognizing patients at higher risk of recurrence and poor outcomes based on these two schemas. Such a system for PaCa has been lacking until recently. This first-of-its-kind study and other works of this group may have had a role in the addition of PaCa to the 8th edition TNM/AJCC (American Joint Committee on Cancer) cancer staging manual for the first time. Validation of the staging system has the potential of helping

guide individualized treatment protocols for patients with varying risk of recurrence or death and laying the foundation for future outcome research in PaCa.

RELEVANT ADDITIONAL STUDIES

For over two decades, determining the outcomes of PaCa have been attempted by designing classification systems using pathological features and the TNM type of classification. Initially, Shaha et al.[9] in 1999 proposed a TNM type of classification system for PaCa which utilized tumor factors like size and the presence of peritumoral invasion to predict outcomes. This staging system was, however, unable to predict the long-term recurrence and survival outcomes in subsequent studies.[10–12] In 2010, Talat and Schulte[1] proposed a new TNM-type classification system for PaCa and a binary low risk–high risk classification, which were more predictive of recurrence and long-term survival. The authors found that capsular and vascular invasion and the patterns of invasion into surrounding structures risk-stratified these patients and incorporated these histological characteristics into a TNM-type classification. Capsular invasion has more diagnostic value, and its prognostic significance has yet to be confirmed.[13] Talat and Schulte.[1] in their study evaluated all three classification systems. The staging system proposed by Shaha et al in 1999 was also compared in this study, which showed that tumors larger than 3 cm had a marginally higher risk of recurrence (RR 1.53, 95% CI 1.0–2.1; $p < 0.05$), through did provide a prediction of death. Advanced tumor stages (III, IV) did not reliably predict worse outcomes compared to lower stages (I or II). When patients were categorized into having low-risk versus high-risk cancers according to risk stratification, the presence of an advanced stage carried a 3.5-fold higher risk of recurrence (95% CI 1.5–8.0; $p < 0.0001$) and a 4.9-fold higher risk of death (95% CI 1.2–19.5; $p = 0.005$). The TNM staging system reported by Schulte found a stepwise worsening of outcomes with advancing patient stage. For those patients in whom an exact stage could be determined, recurrence was observed in 14%, 41%, and 66% of stage I, II, and III cases, respectively, as opposed to 83% for patients with unknown stages. Overall, death occurred in 6%, 23%, and 34% of stages I, II, and III cases, respectively, as opposed to 51% of patients with unknown staging. The RR of death from PaCa was 2.3-fold higher (95% CI 1.6–3.2; $p < 0.0001$) in patients without sufficient staging information compared with those assigned to stage I–IV.

The proportion of PaCa cases among PHPT patients is relatively higher in studies from low- and middle-income countries, but has been reported to fall when more asymptomatic PHPT patients are treated.[5] Various factors predictive of a poor disease prognosis have been reported in multiple studies and include older age, male sex, larger tumor size, presence of distant metastases, higher serum calcium at diagnosis, and loss of parafibromin expression.[1,14–16] Silva-Figueroa et al. proposed a prognostic scoring system to predict recurrence-free survival in PaCa patients that combined preoperative calcium levels (>15 mg/dL), age (>65 years), and vascular invasion. These characteristics objectively stratified cases, identified those individuals at higher risk of recurrence, and suggested aggressive surveillance or adjuvant treatment for such high-risk patients.[17] Identification of a CDC73 mutation, and its prognostic significance, has the added advantage of identifying a germline mutation that prompts genetic screening of family members. Loss of parafibromin expression has been found to have a greater prognostic significance than CDC73 mutations.[18]

In summary, PaCa is a rare endocrine malignancy that is associated with high recurrence rates of up to 50% but a favorable long-term outlook (60–70% 10-year OS). Given its rarity and nonspecific presentation, preoperative diagnosis of PaCa is often missed, and it is frequently understaged and undertreated. A robust classification system that combines clinical, biochemical, and tumor factors to predict outcomes for PaCa patients is much needed, and Schulte et al. have well addressed this need in what we consider a landmark paper.

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