Innovations in Modern Endocrine Surgery

Michael C. Singer
David J. Terris
Editors

Springer

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ISBN 978-3-030-73950-8 ISBN 978-3-030-73951-5 (eBook)
https://doi.org/10.1007/978-3-030-73951-5

This Springer imprint is published by the registered company Springer Nature Switzerland AG
The registered company address is: Gewerbestrasse 11, 6330 Cham, Switzerland

David J. Terris

To my family, friends, colleagues, trainees, and the many patients who were so generous in allowing me to learn from them over three decades. And finally, a special acknowledgment to three very important people in my life – Amy, Bill, and Dick

Michael C. Singer

To my parents, David and Judy Singer, and in-laws, Sam and Brenda Gewurz, whose common values of love of family, concern for the welfare of others, and living lives of principle have provided a framework for my personal and professional life. Your impact knows no bounds.

Preface

Over the past two decades, the care of patients with thyroid and parathyroid diseases has been transformed. Molecular, diagnostic, radiological, and surgical developments that touch on all elements of the care of these patients have resulted in improved outcomes and satisfaction.

While surgeons performing thyroid and parathyroid surgery may endeavor to remain abreast of all the advances in the field, staying current can be challenging. This book was conceived as a single resource for surgeons seeking to understand the latest developments and trends in the field. This book is the first to focus on the range of innovations that have been critical to the emergence of modern endocrine surgery. Fortunately, the authors of many of the chapters are the experts who have been the primary proponents of the individual innovations. This allows them to place these developments in their proper context, crucial to understanding their value and proper application.

Equipped with the knowledge provided by this text, surgeons can assess their own practice and choose to integrate innovations that may improve their patients' outcomes.

Detroit, MI, USA — Michael C. Singer
Augusta, GA, USA — David J. Terris

Contents

Part I Diagnosis and Preoperative Work-up of Thyroid Disease

1 Ultrasound for Thyroid Nodule Risk Stratification 3
Poorani N. Goundan and Stephanie L. Lee

2 Molecular Assessment of Thyroid Nodules 21
Mayumi Endo, Dina M. Elaraj, Neda A. Moatamed, and Richard T. Kloos

3 Active Surveillance for Thyroid Cancer 55
Caitlin B. Iorio and David C. Shonka Jr

4 Hemithyroidectomy for Differentiated Thyroid Cancer 67
Jorgelina Luz Guerra and R. Michael Tuttle

5 Neoadjuvant Therapy for Anaplastic Thyroid Carcinoma 81
Sagar Kansara, Maria E. Cabanillas, and Mark Zafereo

6 Nonoperative Thyroid Ablation Techniques for Benign Thyroid Nodules 89
Brian Hung-Hin Lang and Woojin Cho

Part II Diagnosis and Preoperative Work-up of Parathyroid Disease

7 Localization Studies for Hyperparathyroidism 107
Steven Craig, Adrian Harvey, and Janice L. Pasieka

8 Subtle Variants of Hyperparathyroidism: Normohormonal Hyperparathyroidism 125
Julia E. Noel, David L. Steward, and Lisa A. Orloff

9 Subtle Variants of Hyperparathyroidism: Normocalcemic Hyperparathyroidism 137
Rohit Ranganath, Kendall F. Moseley, and Ralph P. Tufano

10 Indications for Parathyroidectomy 149
Sara M. Wing, Michael Lui, Kepal N. Patel, and Brendan C. Stack Jr

Part III Surgical Adjuncts

11 Intermittent Neuromonitoring of the Recurrent Laryngeal Nerve 157
Erin P. Buczek, Dipti Kamani, and Gregory W. Randolph

12 Continuous Neuromonitoring of the Recurrent Laryngeal Nerve 173
Marcin Barczyński and Rick Schneider

13 Neuromonitoring of the Superior Laryngeal Nerve 185
Andre S. Potenza and Claudio R. Cernea

14 Advanced Energy Devices 197
Jina Kim and Quan-Yang Duh

15 Parathyroid Gland Fluorescence Imaging 207
Richard H. Law and Michael C. Singer

16 Intraoperative PTH Monitoring 219
Ahmad M. Eltelety and David J. Terris

Part IV Surgical Techniques

17 Minimally Invasive Video-Assisted Parathyroidectomy (MIVAP) and Minimally Invasive Video-Assisted Thyroidectomy (MIVAT) 235
Paolo Miccoli and Michele N. Minuto

18 Robotic Transaxillary Thyroidectomy 245
Ehab S. Alameer, Grace S. Lee, and Emad Kandil

19 Transoral Thyroidectomy 257
Mohammad Shaear and Jonathon O. Russell

Part V Postoperative Management

20 Ambulatory Endocrine Surgery 271
Kelvin Memeh and Peter Angelos

21 Postoperative Calcium Management 283
Guy Slonimsky and David Goldenberg

Index 295

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Part I
Diagnosis and Preoperative Work-up of Thyroid Disease

Chapter 1
Ultrasound for Thyroid Nodule Risk Stratification

Poorani N. Goundan and Stephanie L. Lee

Introduction

Ultrasound (US) is the imaging modality of choice and the standard of care for evaluating thyroid nodules. While thyroid nodules are a common occurrence, only about 5% are malignant. Historically, in order to stratify a patient's risk for thyroid cancer, physicians would consider their clinical history, family history, and physical examination. However, these factors provided only a limited ability to discriminate between benign and malignant nodules. The development of a noninvasive tool for cancer risk assessment became a necessity to reduce the number of invasive procedures including biopsy and surgical resection [1, 2].

In the 1950s, Blume and colleagues showed that one of the earlier versions of US technology, A-mode scanning, could provide the distance of a refractile surface to a US probe. Based on this capability, the detection and measurement of a single dimension of a thyroid nodule was possible [3]. The introduction of B-mode imaging allowed the creation of two-dimensional images by combining serial A-mode images [4]. It was in the 1960s that US technology was first applied to the evaluation of thyroid nodules. Fujimoto et al., in 1967, published their data on 184 patients and described four basic patterns of thyroid nodules: cystic, sparsely spotted, increased attenuation without internal echos and malignant [5]. Essentially, the technology at the time could identify large nodules, but did not provide adequate resolution to discriminate between benign and malignant nodules.

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M. C. Singer, D. J. Terris (eds.), *Innovations in Modern Endocrine Surgery*,
https://doi.org/10.1007/978-3-030-73951-5_1

The development and application of gray-scale imaging in the 1970s allowed for more granular characteristics of thyroid nodules to be recognized and improved correlation with histopathologic findings [6, 7]. Over the following decades, gray-scale US has been further refined with the development of higher-frequency probes and post-imaging enhancement such as tissue harmonic and compound spatial imaging [8, 9]. In an effort to further increase the discriminatory value of US and aid in estimating malignancy risk, gray-scale imaging has been combined with other US modalities, including Doppler analysis and elastography, and with fine-needle aspiration (FNA). To consolidate our knowledge regarding US features and the risk of cancer, several risk stratification systems have been developed [10–14].

This chapter will discuss the current role thyroid US plays in the management of thyroid nodules and will highlight possible future directions of this technology.

Ultrasound Setting and Image Acquisition

In order to obtain quality and consistent images, patient positioning and US settings need be optimized prior to acquiring US images. The patient's neck should be hyperextended, which may be facilitated by placing a pillow behind their shoulders. High-resolution US typically uses US frequencies between 10 and 15 MHz or higher for imaging the thyroid gland. The focus and frequency of the sound waves and gain should be adjusted to the level of structures being imaged. Adjustment of the focus to the depth of the nodule is critical to detect and characterize the fine details of the nodule, echogenicity and margins of a nodule (Fig. 1.1). A complete US exam of the thyroid gland includes visualization of thyroid and perithyroidal structures and characterization of the cervical lymph nodes. A final US report should include a description of the thyroid gland parenchyma and its dimensions, a detailed description of relevant thyroid nodules, and information regarding the presence or absence of abnormal cervical adenopathy.

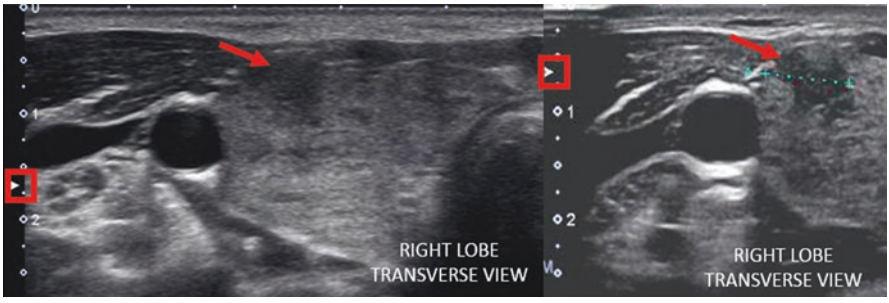


Fig. 1.1 Difference in quality and resolution of images between (**a**) sub-optimal US settings using a 14 MHz probe and incorrect focus (red box) and (**b**) optimal US settings using an 18 MHz probe and correct focus (red box) in a thyroid gland with a hypoechoic anterior nodule with infiltrative margins (arrow) with a heterogeneous background of Hashimoto's thyroiditis

Gray-scale Ultrasound Characteristics of Thyroid Nodules

Individual US characteristics have variable sensitivity, specificity and positive predictive value (PPV) for thyroid cancer (Table 1.1) [15–19]. The description, US examples, and interpretation of cancer risk of these characteristics are discussed in Table 1.2. High-risk US features for malignancy include a solid composition, hypoechogenicity, taller than wide dimensions, irregular margins, and microcalcifications. Interrupted peripheral macrocalcification, particularly when seen with extranodular soft tissue extrusion, is a high-risk US feature, while isolated intranodular macrocalcification is not [20, 21]. Most US features that we associate with thyroid cancer identify the most common type of thyroid cancer, papillary thyroid cancer (PTC), in particular the classic type. Other less prevalent thyroid cancers including follicular thyroid cancers (FTC), follicular variants of PTC, and noninvasive follicular neoplasms with papillary-like features (NIFTP) may be hypoechoic but are more often iso- or hyperechoic and are not associated with microcalcifications [18, 22, 23]. While medullary thyroid cancers tend to be hypoechoic and contain intranodular calcifications, their US features are less well defined [24].

There are several US features that are associated with benign nodules (Figure 1.2a–c). Purely cystic or spongiform nodules never or rarely require FNA, as their risk of malignancy is very low. A colloid comet, a US artifact due to reverberation of echo signals in colloid, is a benign finding. However, these can be difficult to distinguish from hyperechoic, non-shadowing microcalcifications, which are potentially associated with cancer. Importantly, indistinct margins must be distinguished from infiltrative margins. While indistinct margins are not specifically a characteristic of low-risk thyroid nodules, they usually occur in confluent isoechoic adenomatous nodules and are not a high-risk feature for malignancy.

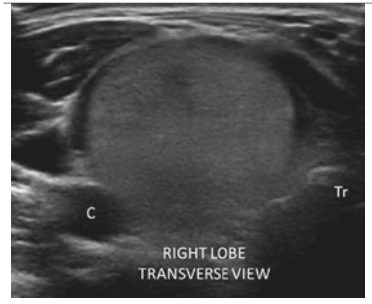
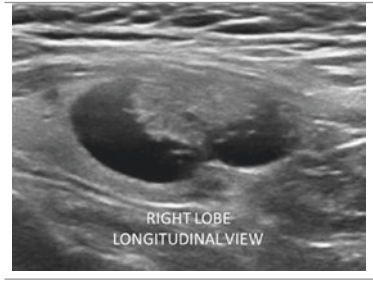
US interpretation is both instrument and operator dependent. Studies have demonstrated interobserver variability that is more evident with certain US features such as nodule volume, margins, and the presence of microcalcifications [25–27]. To try to minimize this interobserver variability seen when interpretation is done by a physician, the use of machine learning for US characteristic and pattern recognition has begun to be investigated [28, 29].

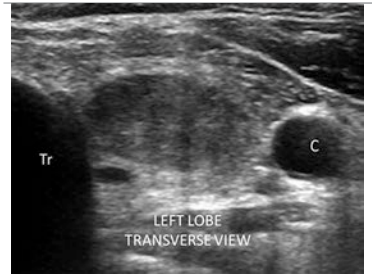
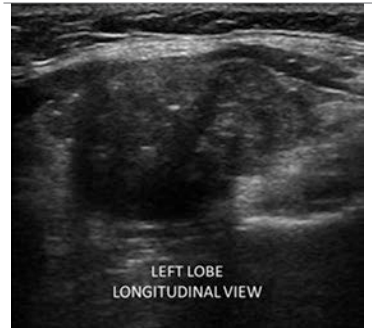
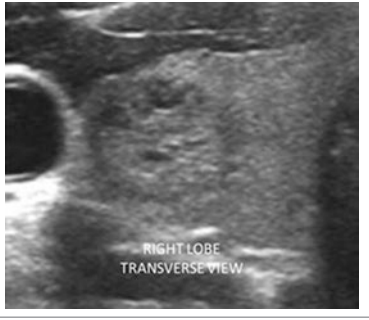
Table 1.1 Individual ultrasound characteristics of thyroid nodules and risk for thyroid cancer*

Nodule characteristic	Sensitivity	Specificity	PPV
Hypoechogenicity	68–87%	43–81%	11–61%
Marked hypoechogenicity (similar to strap muscle)	27–69%	92–98%	68–96%
Solid consistency	89–91%	33–58%	26–39%
Microcalcification	36–59%	86–98%	39–85%
Macrocalcification	2–10%	96–98%	25–65%
Irregular/microlobulated margins	48–84%	83–92%	30–81%
Taller than wide configuration on transverse view	32–64%	91–100%	67–100%

* [15–19]

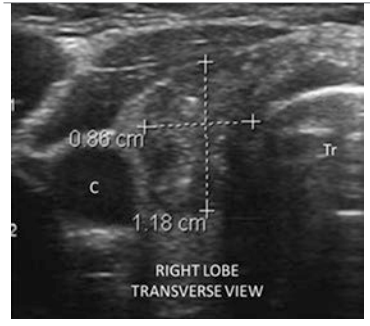
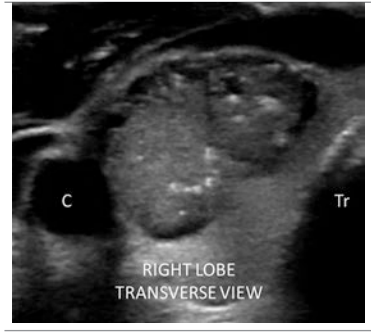
Table 1.2 Interpretation of Individual "high-risk" thyroid nodule US characteristics

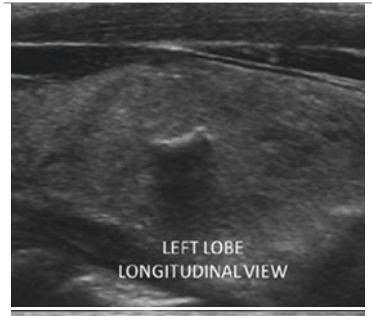
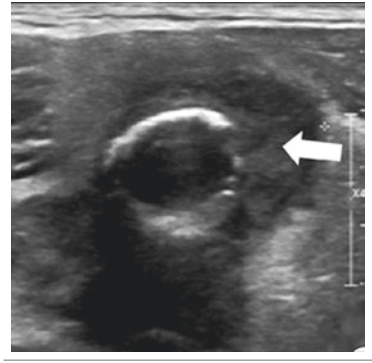
Ultrasound characteristic	Definition	Interpretation/discussion
Solid composition		
	Entire nodule has a predominantly solid component	This is not specific for thyroid cancer, but nearly all cancers are solid
	If a mixed solid cystic nodule, assess the characteristics of the solid component, and estimate the angle made between nodule wall. Nodules with an acute angle (<90°) between nodule wall and solid component are likely high risk than if an obtuse angle is present	

Hypoechogenicity		
	Isoechoic is defined as equal echogenicity of the normal thyroid parenchyma and the submandibular gland Mild hypoechogenicity is when nodule echogenicity is reduced compared to surrounding thyroid parenchyma Marked hypoechogenicity is when the nodule echogenicity is similar to that of the overlying strap muscles	In conditions when the thyroid parenchyma is hypoechoic, detection of a hypoechoic nodule, especially one with infiltrative margins, can be difficult
Irregular margins		
	Either microlobulated or infiltrative margins	An indistinct margin, referring to a nodule margin that is not clearly visualized, is not an irregular margin and is not a high-risk US feature. It is often found in adenomatous nodules 

(continued)

Table 1.2 (continued)

Ultrasound characteristic	Definition	Interpretation/discussion
Taller than wide configuration		
	This is usually described in the transverse view. It refers to the anteroposterior diameter being equal to or greater than the transverse diameter of the thyroid nodule (AP ≥ TR)	
Microcalcification		
	Microcalcification are non-shadowing punctate hyperechoic foci	There are many other hyperechoic genic foci seen in thyroid nodules (such as comet tail artifact and focal fibrosis) that can be mistaken for microcalcification

Macrocalcification		
 	Macrocalcification appears as larger hyperechogenic US reflection with posterior shadowing	Isolated intranodular macrocalcification is not a high-risk feature except for medullary thyroid cancer Interrupted peripheral rim of calcification with soft tissue extrusion (white arrow) is a concerning US feature

C carotid artery, *Tr* trachea

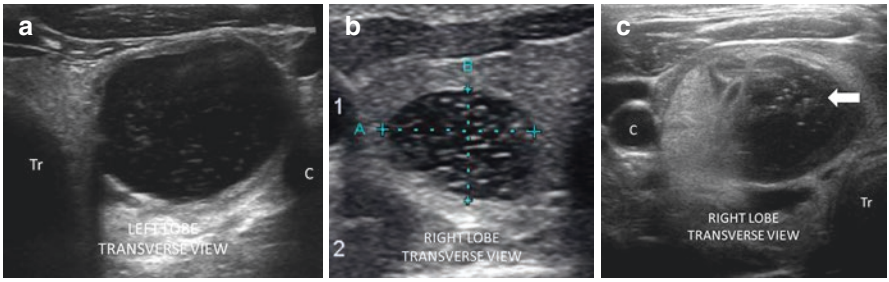


Fig. 1.2 (**a**–**c**) Low-risk thyroid nodule ultrasound feature. (**a**) Cystic nodule: an anechoic or hypoechoic lesion with posterior enhancement and no solid tissue. (**b**) Spongiform nodule: nodule with more than 50% of the nodule occupied by microcystic spaces with linear posterior wall reflection enhancement. (**c**) Comet tail artifact: a reverberation artifact seen within a cystic nodule

Doppler Flow in Thyroid Nodule Evaluation

Doppler flow imaging (Doppler) provides additional information about the vascularity of thyroid nodules. Color flow Doppler images indicate direction and speed of vascular flow within tissue. Power Doppler, on the other hand, does not take into consideration differences in frequency shifts and represents the total amount of flow irrespective of direction. Power Doppler is more sensitive in picking up low flow and is favored by some [30]. However, it also has a higher background signal, and some practitioners consequently prefer the higher specificity of color flow Doppler analysis.

Thyroid nodule vascularity can be graded on a scale of 1–4 (Figure 1.3a–d): no flow (grade 1), peripheral flow (grade 2), low central flow (grade 3), and high central flow (grade 4). In 2010, Moon et al. published data showing that vascularity was not a helpful predictor for malignancy [31]. This was conflicted with the results of prior studies. In 1083 nodules, intranodular vascularity was present in 17% and absent in 60% of malignant nodules vs. 31% and 60%, respectively, in benign nodules. The cancers in this study were predominantly PTC and included small nodules (i.e., less than 1 cm). Most studies evaluating vascular flow of thyroid malignancies have a predominance of classical variant of PTC, which can make the sensitivity of intranodular vascular flow low as a marker for malignancy. When looking specifically at follicular lesions, there is evidence to suggest a role for Doppler detection of intranodular vascular flow [32, 33]. In one study, in 305 nodules that were classified as follicular lesions on FNA, intranodular flow was seen in only 5% of benign adenomatous nodules (grade 3 vascularity), 34% of follicular adenomas, and 86% of follicular carcinomas (grade 3–4 vascularity) [32]. Other studies have, however, showed considerable overlap between the vascular pattern of benign lesions and follicular cancers and a lack of a predictive value of vascular distribution [34, 35].

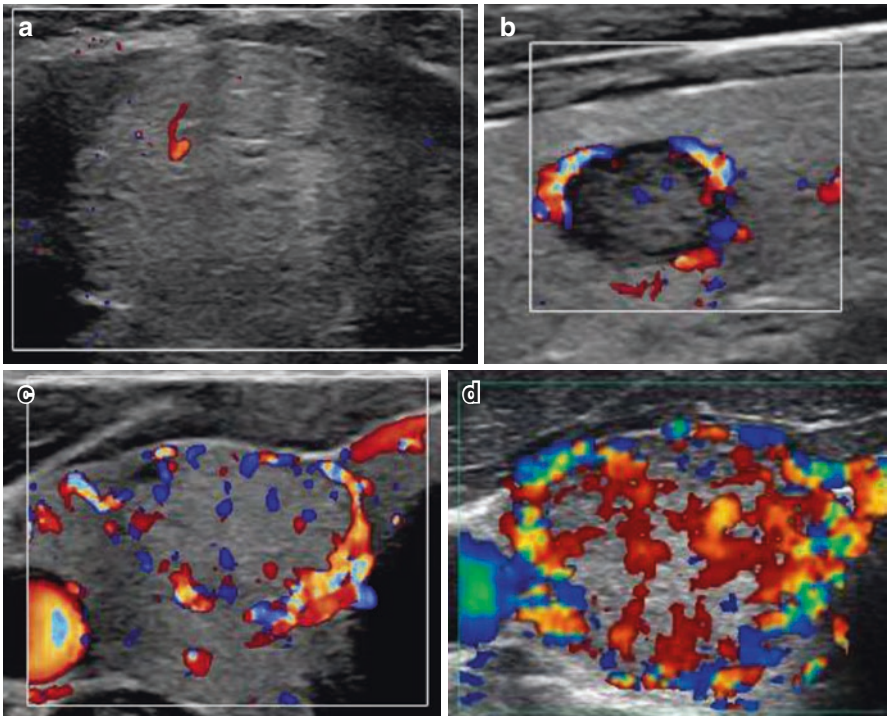


Fig. 1.3 Vascular grade of thyroid nodules. (**a**) Grade 1: No or scant vascularity. (**b**) Grade 2: predominantly perinodular vascularity. (**c**) Grade 3: low intranodular vascular flow. (**d**) Grade 4: high intranodular vascular flow

Elastography

Elastography assesses the degree of stiffness of tissue utilizing sound waves to measure the amount of compression from external pressure. In strain elastography, the most commonly used technique relied on intermittent manual external pressure being applied with the US probe. This introduced a significant limitation of being operator dependent. Subsequently, quantitative elastography techniques have been developed to reduce this confounding factor. When a strain ratio is calculated from the mean strain of the nodule and the surrounding tissue, there is some improvement in interobserver variability [36]. Elasticity contrast index, which utilizes the pulsation of the adjacent carotid artery as a source of pressure, is another semiquantitative method developed and studied in thyroid nodules [37]. Shear wave elastography utilizes an ultrasonic pulse from the probe rather than manual compression to obtain a numerical value for stiffness based on change in wave propagation speed. This method has been demonstrated to be less operator dependent and more reproducible [38].

Studies have shown the utility of combining elastography with conventional gray-scale US characteristics in risk assessment. When elastography was combined

with five conventional US risk characteristics (hypoechogenicity, microcalcification, taller than wide configuration, irregular margins, and intranodular vascularization), the overall sensitivity improved (compared to analysis with only gray-scale US characteristics) from 85% to 97%, and the negative predictive value increased from 91% to 97% [39]. Similarly, in 142 nodules with indeterminate cytological classification on FNA, elastography demonstrated a specificity of 91.8% but a sensitivity of 96.8% [40]. Overall, multiple studies have demonstrated the potential use of elastography as a predictor of benign disease in thyroid nodules. In a prospective study looking at the use of shear wave elastography only, a threshold of 3.45 m/s produced a sensitivity of 79.3% and specificity of 71.5%. The cancer prevalence in the cohort was 11.5%, and the PPV and negative predictive value (NPV) were found to be 26.7% and 96.3%, respectively [41].

While elastography may provide additional, useful information, it does have drawbacks. In addition to interobserver variability, shear wave elastography does have a marked operator learning curve. Additionally, both strain and shear wave elastography cannot be used when significant cystic areas or calcification is present in thyroid nodules. Furthermore, their results are affected by nodule depth and surrounding tissue fibrosis, which limits the broad utility of these imaging methods.

Risk Stratification System

Recognizing that sensitivity and specificity of individual US features are not adequate to predict benignity or malignancy of thyroid nodules, risk stratification systems, which incorporate multiple US features, have been developed. Several of these systems, which were based on the Breast Imaging Reporting and Data System (BI-RADS) system followed for breast imaging, adopted the name Thyroid Imaging Reporting and Data System (TI-RADS). One of the earliest versions of this was developed and described by Horvath and colleagues in 2009 [42]. Since then, several research groups and professional societies have developed different iterations of TI-RADS. The American College of Radiology (ACR) TI-RADS assigns points for individual US features, and the total score determines the risk category – a higher score indicating a higher risk for cancer [11].

In contrast, the American Thyroid Association (ATA) guidelines rely on pattern recognition in determining cancer risk in a nodule [12]. This is similar to the pattern recognition approach taken by the Korean Society of Radiology (K-TI-RADS), the European Thyroid Association (EU-TI-RADS) and the American Association of Clinical Endocrinologist (with the American College of Endocrinology and Associazione Medici Endocrinologi Medical) [10, 13, 14]. All methods follow the same principle of assigning a higher risk category for nodules with a greater number of high-risk US features. When combined with a threshold diameter to consider biopsy, these systems are designed at improving diagnostic accuracy of US and FNA and reducing the number of unnecessary thyroid nodule biopsies performed [10–14]. It is important to point out that, as noted previously, the high-risk US

Table 1.3 American Thyroid Association stratification of sonographic patterns and risk of malignancy

Sonographic pattern	US feature
High suspicion	Hypoechoic echogenicity (solid nodule or solid portion of a partially cystic nodule) with one or more of the following: Irregular margins Microcalcifications Taller than wide dimension Peripheral rim of calcification with soft tissue extrusion Extrathyroid extension Presence of abnormal or suspicious cervical lymphadenopathy
Intermediate suspicion	Hypoechoic solid nodule with smooth margins without other high-risk US features
Low suspicion	Isoechoic or hyperechoic solid nodule or partially cystic nodule with eccentric solid area, without high-risk US features
Very low suspicion	Spongiform or partially cystic nodules without any high, intermediate, or low suspicion US features
Benign	Purely cystic nodule

characteristics used to determine if a nodule requires biopsy are more specific for the hypoechoic classical PTC compared to the more isoechoic follicular variant PTC, the more isoechoic follicular thyroid cancer, and NIFTP.

When comparing the two commonly used thyroid nodule risk stratification systems in the Unites States, i.e., the ATA US risk stratification and ACR TI-RAD (Tables 1.3, 1.4, and 1.5) [11, 12]:

(a) Ahmadi et al. showed in their review of 323 thyroid nodules (27.2% malignant) the sensitivity and specificity for detection of cancer of the ATA guideline recommendations to be 77.3% and 76.6%, respectively, and the ACR TI-RADS 78.4% and 73.2% [43]. Gao et al. reviewed 2455 nodules (66.1% malignant) and determined a higher sensitivity of 95.5% for the ATA guidelines compared to 81.6% for the ACR TI-RADS [44]. In general, based on statistical analysis, a risk stratification system that combines multiple US features compared to individual high-risk characteristics will increase specificity but also reduce the sensitivity of the test. This results from the fact that while few thyroid cancers will have all the high-risk sonographic features, those that do have these characteristics are very likely to be malignant.

(b) The ATA system utilizes US patterns to classify nodules into risk categories. Because of this, several nodules are not considered classifiable if the definition of each risk category is strictly followed. Nodules in this "unclassified" category include iso- or hyperechoic nodules with additional high-risk US characteristics such as irregular margins or microcalcification. In one study, this represented 54 of 1077 thyroid nodules that were found to have an increased risk (OR 7.2, CI: 2.44–21.24) for high-risk cytology compared to the nodules with lower US suspicion features [45].

Table 1.4 Summary of ACR Thyroid Imaging Reporting and Data System (TI-RADS)

Step one: Assign points for US feature			TI-RADS category
Composition (choose one)	Cystic or spongiform [a](zero points)/mixed solid and cystic (one point)/solid (two points) (if composition cannot be determined, assign two points)	Add points from each category	TR1 (benign): zero points
Echogenicity (choose one)	Anechoic (zero points)/hyper-or isoechoic (one point)/hypoechoic (two points)/very hypoechoic (three points) (if echogenicity cannot be determined, assign one point)		TR2 (not suspicious): two points
Shape (choose one)	Wider-than tall (zero points)/Taller than wide (three points)		TR3 (mildly suspicious): three points
Margin (choose one)	Smooth or ill defined (zero points)/lobulated or irregular (two points)/extrathyroidal extension (three points) (if margin cannot be determined, assign zero points)		TR4 (moderately suspicious): four to six points
Echogenic foci (all that apply)	None or large comet tail artifacts (zero points)/macrocalcification (one point)/peripheral (rim) calcifications (two points)/punctate echogenic foci (three points)		TR5 (highly suspicious): ≥ seven points

[a]If spongiform, do not add additional points for echogenicity, shape, margin or echogenic foci

Table 1.5 Comparison of ATA and ACR TI-RADS thyroid nodule risk stratification systems and biopsy recommendations (with theoretial risk of malignancy)

ATA (2015)		ACR TI-RADS (2017)	
Benign (0%)	No FNA	TR1: benign (<2%)	No FNA
Very low suspicion (<3%)	Consider FNA if ≥2 cm or observation	TR2: not suspicious (<2%)	No FNA
Low suspicion (5%–10%)	FNA if ≥1.5 cm	TR3: mildly suspicious (5%)	FNA if ≥2.5 cm Follow if ≥1.5 cm (US at 1 and 3 years)[b]
Intermediate suspicion (10%–20%)	FNA if ≥1 cm	TR4: moderately suspicious (5%–20%)	FNA if ≥1.5 cm Follow if ≥1 cm (US at 1, 2, 3, and 5 years)[b]
High suspicion (>70%–90%)	FNA if ≥1 cm	TR5: highly suspicious (at least 20%)	FNA if ≥1 cm Follow if ≥0.5 cm (US every year for 5 years)[b]

[a]If adenopathy suspicious for metastatic cancer is seen on US, both the ACR TI-RADS and ATA guidelines recommend FNA of the lymph node [11, 12]

[b]Can stop imaging at 5 years if there is no change in nodule size; if a nodule's ACR TI-RADS level increases on follow-up imaging, then repeat US in 1 year irrespective of initial TI-RADS level

(c) Both the ATA system and ACR TI-RADS suggest a size threshold of 1 cm for recommending a biopsy for a nodule in their highest-risk categories (i.e., high suspicion and TR5, respectively). Sub-centimeter tumors, in the absence of local invasion or adenopathy or distant metastasis, often are indolent [46].

(d) The ATA guideline provides a lower size threshold, of 1.5 cm and 1 cm, regarding when to recommend biopsy for low and intermediate suspicion nodules. For equivalent ACR TI-RADS categories of mildly suspicious TR3 and moderately suspicious TR4, biopsy is recommended for nodules greater than 2.5 cm and 1.5 cm, respectively. Multiple studies have demonstrated that the ACR TI-RADS results in a greater number of nodules in which biopsies are avoided compared to the ATA system. This relative reduction by the ACR TI-RADS has been reported to be around 40%–50%, with a false negative rate between 2% and 3% [44, 47]. In one study, however, in nodules which would not have been biopsied if following TI-RADS, the malignancy rate was as high as 11.3%. Interestingly, the rate was similar when the ATA guidelines were applied (10.1%). These false-positive cases tend to be iso- or hyperechoic nodules, as described earlier. Of note, data suggests that papillary and follicular thyroid cancers that are >2–2.5 cm in size have been associated with an increased cumulative risk for distant metastasis [48, 49].

(e) As part of the thyroid nodule evaluation guidelines, the ATA recommends thyroid scintigraphy if TSH levels are low. This is not outlined in the ACR TI-RADS and can lead to biopsy of "hot" nodules that have to have a low risk of malignancy. In this setting, some have expressed concerns about an increased risk of false-positive cytology (atypia of undetermined significance/follicular lesion) on FNAs performed on autonomous nodules. However, this has not been seen consistently [50, 51].

(f) The ACR TI-RADS recommends serial US for TR3–5 nodules that do not meet the criteria for FNA for up to 5 years at varying frequency depending on the risk category. If there is stability in size and US characteristics, the US can be stopped at 5 years. It does not provide specific recommendations regarding follow-up for nodules with a prior benign biopsy.

The ATA guidelines do address this scenario. Following a benign biopsy, they recommend repeating a US for nodules with a high suspicion pattern in 1 year and for nodules with low to intermediate suspicion patterns in 1–2 years. For nodules with a very low suspicion pattern (spongiform or cystic) and for nodules with two benign biopsy results, follow-up US may not be required. In a nodule with a benign biopsy result, suspicious US features rather than growth should possibly determine the need for repeat biopsy [52]. It should be noted that the serial US exams recommendations in the ATA and TI-RADS classification systems are for risk of malignancy and not for sequential growth of a benign nodule. Although it is likely that low risk subcentimeter nodules do not require long-term followup, larger nodules have a potential for growth and developement of obstructive symptoms and require intermittent evaluation for growth [53].

(g) Both the ATA guidelines and ACR TI-RADS recognize extrathyroidal extension as a high-risk feature that should place a thyroid nodule in a higher risk category. Nodule size would then determine if a biopsy would be indicated. The authors, however, recommend biopsy of any suspicious nodule with extrathyroidal extension irrespective of its size. Biopsy of abnormal cervical lymph nodes, if detected while evaluating a thyroid nodule, is recommended regardless of the nodule size.

(h) The ATA guidelines and ACR TI-RADS do not incorporate elastography or vascularity as a tool in the assessment of thyroid nodules. In a stratification system developed by Russ and colleagues, a five-tier TI-RADS classification system that included the use of elastography with gray-scale US characteristics demonstrated a slightly improved sensitivity of 98.5% (in 991 cases) compared to 95.7% when only gray-scale US characteristics were included (in 3658 cases) [54]. The use of elastography has not been universally adopted because of the cost of the equipment and operator and machine variability. Some classification systems, however, such as the French thyroid TI-RADS, have included it [55, 56].

Conclusion

The current evaluation of thyroid nodules includes assessment of thyroid function, gray-scale characteristics of a thyroid nodule combined with other US modalities, including Doppler analysis and elastography, and with fine-needle aspiration. The TI-RADS thyroid nodule risk assessment reduces biopsies compared to the ATA system but may be associated with more missed cancers (follicular thyroid cancer, follicular variant of PTC and NIFTP that are usually isoechoic). Newer techniques including contrast-enhanced US, three-dimensional US imaging, and quantitative US have been or are currently being studied to expand the sonographic techniques to evaluate thyroid nodules [57–59]. Many groups are exploring the application of deep machine learning and artificial intelligence to improve the diagnostic accuracy of the current risk stratification systems and to avoid errors in interpretation of images [28, 29]. However, despite that gray-scale US includes machine and operator limitations, it remains the imaging modality of choice for evaluating thyroid nodules for the risk of malignancy.

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Chapter 2
Molecular Assessment of Thyroid Nodules

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Introduction

Most thyroid nodules are benign, but 10% represent cancer; hence, if clinically or sonographically indicated, fine-needle aspiration (FNA) is warranted [1, 2]. In the United States, it is estimated that 540,000 FNA procedures occurred in 2018 [3]. While a definitive benign or malignant diagnosis is sought, approximately 15%–30% of thyroid nodules cannot be definitively resolved cytologically and are reported as "indeterminate" based on the widely implemented The Bethesda System for Reporting Thyroid Cytopathology (TBSRTC) [4]. These nodules are a management challenge as they have more than a minimal risk of cancer, and historically, they underwent diagnostic surgery despite the majority proving to be benign. Here, we discuss current cytological nomenclature, review cellular genomics, assess current genomic tests for cytologically indeterminate nodules, consider surgical options, explore the role of genomics among suspicious and malignant cytology categories, and finally consider future directions.

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M. C. Singer, D. J. Terris (eds.), *Innovations in Modern Endocrine Surgery*,
https://doi.org/10.1007/978-3-030-73951-5_2

Cytological Nomenclature of Thyroid Nodules

The Bethesda System for Reporting Thyroid Cytopathology was created in 2007 to establish a standard reporting of thyroid nodule cytopathology, utilizing a six-tier classification system [4, 5]. Using TBSRTC, cytopathologists communicate thyroid fine-needle aspiration (FNA) results with referring and treating physicians. In this system, the diagnostic categories include (I) nondiagnostic or unsatisfactory, (II) benign, (III) atypia of undetermined significance (AUS) or follicular lesion of undetermined significance (FLUS), (IV) follicular neoplasm (FN) or suspicious for a follicular neoplasm (SFN), (V) suspicious for malignancy, and (VI) malignant [4]. The estimated risk of malignancy and recommended management options were included in TBSRTC. An update to TBSRTC [6] addressed the introduction of molecular testing to thyroid FNAs and the newly described entity of noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP) [7]. The 2017 revision reaffirms that all thyroid FNA reports should begin with one of the six diagnostic categories. The risk of malignancy in each category is estimated when considering NIFTP as a benign lesion and also when considering it as a malignancy [6]. Notably, the option of molecular testing was added for Bethesda III and IV categories [6].

Bethesda categories III and IV of thyroid nodules encompass the indeterminate group and are diagnostically challenging for pathologists. Bethesda III (AUS/FLUS) is reserved for specimens that contain follicular cells with architectural and/or nuclear atypia that is not sufficient to be classified as suspicious for a follicular neoplasm, suspicious for malignancy, or malignant (Figs. 2.1 and 2.2).

The hallmark of the FN/SFN (Bethesda IV) specimen is the presence of significant architectural alteration in most of the follicular cells. This can range from crowded/overlapping follicular cells to the presence of microfollicles [4]. This category includes follicular adenomas and follicular carcinomas as their definitive

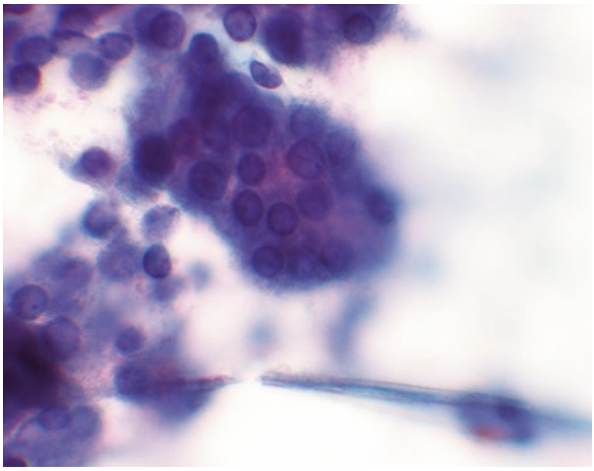

Fig. 2.1 An example of Bethesda III (AUS/FLUS) FNA cytology due to cytological atypia and focal nuclear pallor

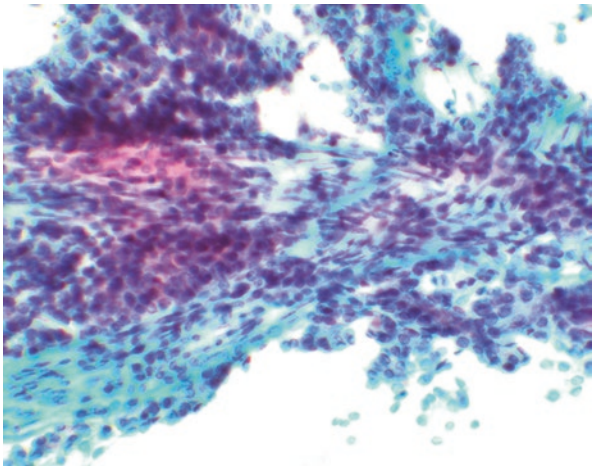

Fig. 2.2 An example of Bethesda III (AUS/FLUS) FNA cytology due to architectural atypia including papillary structures

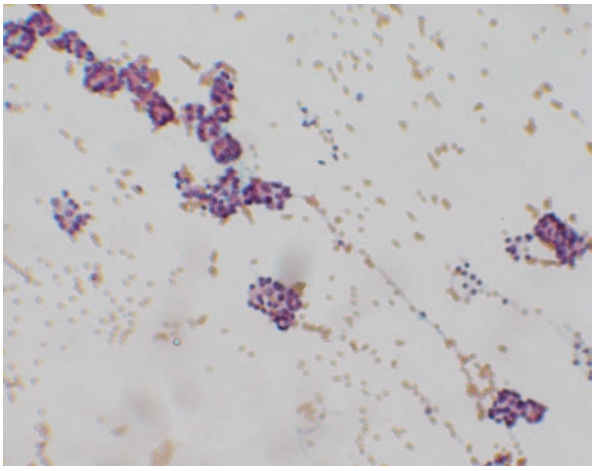

Fig. 2.3 Bethesda IV (FN/SFN) FNA cytology showing microfollicles. Surgical pathology revealed NIFTP

differentiation is only possible with surgical histopathology analysis for capsular and vascular invasion (Fig. 2.3). Further clouding things, fine-needle aspirations of parathyroid adenomas are composed of cells that resemble crowded and overlapping follicular cells that are often categorized as FLUS or FN (Fig. 2.4).

Hürthle cells are deeply eosinophilic and have distinct cell borders and granular cytoplasm. A cytological thyroid sample composed exclusively (or almost exclusively) of Hürthle cells is usually seen in cases with Hashimoto thyroiditis or Hürthle cell hyperplasia in multinodular goiter. However; Hürthle cell neoplasms can have the similar cytological findings. Therefore, these types of FNAs are classified as AUS/FLUS or FN/SFN, Hürthle cell type (Fig. 2.5) [8].

Many primary thyroid malignancies, including papillary and medullary thyroid carcinoma, have distinctive cytological features and can be easily recognized on FNA samples as malignant (Bethesda VI). However, some samples are

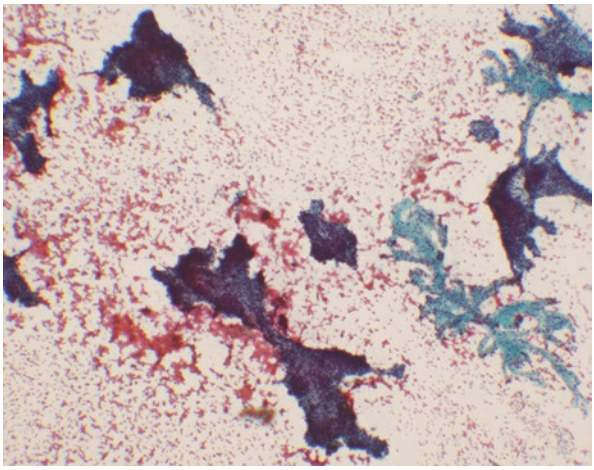

Fig. 2.4 A fine-needle aspiration of parathyroid adenoma that shows crowded sheets of cells resembling follicular cells

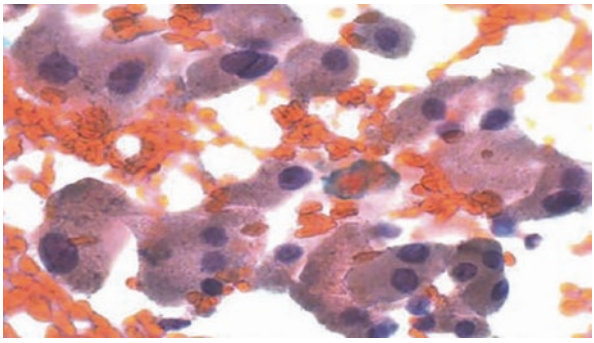

Fig. 2.5 Hürthle cells demonstrating abundant oxyphilic cytoplasm, prominent nucleoli, and a loss of cell polarity

quantitatively and/or qualitatively insufficient for a definitive diagnosis, and these are called suspicious for malignancy cells (Bethesda V). This includes the presence of cytomorphologic (particularly nuclear) features that overlap with other thyroid lesions. Metaplastic changes of benign follicular cells in some cases of Hashimoto thyroiditis can be difficult to distinguish from those of papillary thyroid cancer (PTC). In Bethesda V, cytological findings raise a strong suspicion of malignancy, but the findings are not sufficient for a conclusive diagnosis [4].

The malignant category, Bethesda VI, is for FNA samples with diagnostic cytomorphology features. For example, smears with intranuclear cytoplasmic pseudoinclusions, pale nuclei with powdery chromatin, enlarged and crowded nuclei, and longitudinal nuclear grooves that are arranged in papillae and/or monolayers can confidently be called papillary thyroid carcinoma. This category typically includes carcinomas harboring the *BRAF*^{V600E} variant (Fig. 2.6). Smears with moderate to marked cellularity with plasmacytoid, polygonal, round, and/or spindle-shaped cells and "salt and pepper" chromatin are suspicious for malignancy cells (medullary thyroid carcinoma). With ancillary tests and confirmatory immunohistochemical stains, these samples can be called malignant (Bethesda VI) and subcategorized as medullary thyroid carcinoma

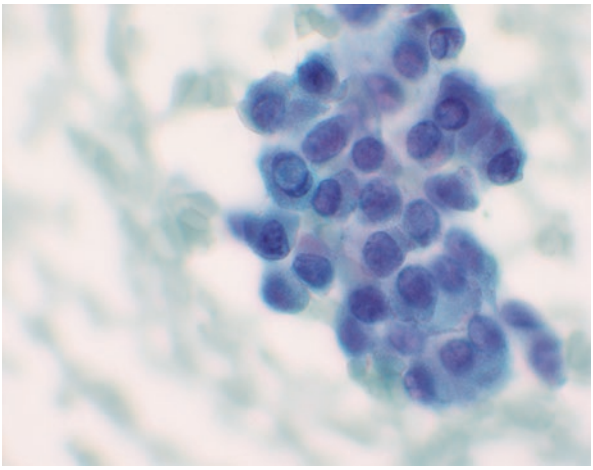

Fig. 2.6 A photomicrograph of Bethesda VI (malignant) FNA cytopathology with papillary thyroid carcinoma. Pale chromatin and intranuclear cytoplasmic inclusion with nuclear grooves are present in this picture

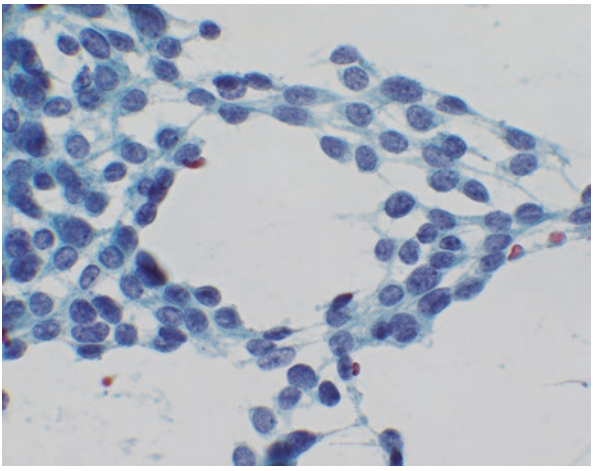

Fig. 2.7 A photomicrograph of a case with medullary thyroid carcinoma. Cells have round nuclei with salt and pepper chromatin

(Fig. 2.7). Still, the cytological diagnosis of medullary thyroid carcinoma often occurs in less than half of medullary thyroid carcinoma patients [9] suggesting that additional tools are needed to ensure that all medullary thyroid cancer patients receive optimal treatment, including their preoperative evaluation and surgical treatment.

Current Trends in the Management of Indeterminate Nodules and Guideline Recommendations

The estimated risk of malignancy in Bethesda III/IV nodules is approximately 25% when NIFTP is considered malignant/warranting surgery [4, 6]. Indeterminate nodules have posed a clinical dilemma. Patients with nodules assigned one of these

Bethesda categories historically underwent diagnostic thyroidectomy. About three-quarters of them were diagnosed on final pathology as having only benign nodules. Medical payers embraced better diagnostic strategies to avoid the cost of unnecessary surgery, while patients and physicians embraced possible avoidance of an invasive procedure and the associated risk of complications [10].

The 2015 American Thyroid Association Management Guideline, 2017 TBSRTC, and National Comprehensive Cancer Network Guideline propose several approaches for management of indeterminate thyroid nodules, including molecular testing and surgery [1, 6, 11]. Among Bethesda III nodules, surveillance, repeat FNA, and a second-opinion review of the cytology specimen are also considered. Unfortunately, there is a relatively high inter- and intra-observer variability in these diagnostic categories, including among expert cytologists [12]. Further, data are not convincing that the risk of malignancy is sufficiently reduced among those with second FNA samples read as benign (Bethesda II) [13–15]. In addition, long-term outcome studies of unoperated nodules with benign results on second FNA are lacking.

A dramatic evolution in our understanding of molecular genomics in the past decade has provided insights, although incomplete, into the genomics of thyroid cancer. This allowed the development of molecular diagnostic tools, discussed later in this chapter, able to differentiate these indeterminate thyroid nodules into suspicious or benign categories.

Machinery of Genomics to Phenotype: DNA, mRNA, ncRNA, and Protein

Here, we briefly review several components of genomics. Carcinogenesis is a complex process that typically involves key (“central”) oncogenes or tumor suppressors but also other internal (diet, inflammation, macrophage, and neutrophil reactive oxygen and nitrogen species) and external factors (smoke, radiation, metals, viruses, genotoxins), epigenetics (noncoding RNA, methylation, histone modification, chromatin remodeling), deficiency of DNA repair, and many “peripheral” genes activities (inherited or acquired). Ultimately, cancer is a disease of dysregulated tissue growth. Genetic and epigenetic changes can occur at many levels, from gain or loss of entire chromosomes, to a mutation affecting a single DNA nucleotide, to silencing or activating a microRNA that controls expression of 100–500 genes. Oncogenes may be normal genes that are overexpressed at high levels or altered genes that have novel properties. Tumor suppressor genes inhibit cell division, survival, or other growth-dampening properties. Tumor suppressor genes are often disabled by cancer-promoting genetic changes. Finally, viruses may contain an oncogene that triggers tumorous growth.

Deoxyribonucleic acid (DNA) carries genetic information that can be passed on from one generation to the next. Genetic information is stored in the sequence of its linked nucleotides. These base pairings provide a mechanism for copying

the genetic information from an existing nucleic acid to the new chain. A gene is a sequence of nucleotides that codes for a molecule that has a function. During gene expression, the DNA is first copied (transcribed) into RNA (collectively known as the transcriptome). The RNA can be directly functional or be the intermediate template for a protein (composed of amino acids) that performs a function. Templates for protein synthesis are made from selected DNA sequences called *exons*, which are transcribed to messenger ribonucleic acid (mRNA). This flow of information is dependent on the genetic code, which is nearly the same in all organisms: a sequence of three nucleotide bases, called a *codon*, specifies an amino acid (translation) for protein assembly.

Splicing of mRNA precursors is required for the maturation of almost all human mRNAs. Alternative splicing, whereby a pre-mRNA can be processed into different mature mRNAs via splice site selection, enables multiple potential protein products to be generated from a single gene. Specific mRNA isoforms produced by alternative splicing have been identified that are selected in cancer owing to their ability to promote neoplastic transformation, cancer progression, and/or therapeutic resistance.

In mammals, although >90% of the DNA is transcribed, only about 2% of the genome is subsequently translated [16]. A functional RNA molecule that is transcribed from DNA but not translated into protein is called noncoding RNA (ncRNA). In general, ncRNAs function to regulate gene expression and play a role in heterochromatin formation, histone modification, DNA methylation targeting, and gene silencing. NcRNAs are divided into two main groups: the short ncRNAs (<30 nucleotides) and the long ncRNAs (lncRNA) (>200 nucleotides).

MicroRNAs (miRNAs) are short ncRNA that regulate mRNA translation or its stability. miRNAs play important roles in cell proliferation and cell death. Hence, its aberrant expression is considered to play a role in carcinogenesis. Dysregulations of miRNAs are considered tumor-specific events that reflect tumor type, behavior, and molecular alteration driving its development. Accordingly, specific miRNAs may have clinical utility as diagnostic and prognostic markers or therapeutic targets. In cancer tissues, overexpressed miRNAs that act as oncogenes are termed onco-miRs, while downregulated miRNAs are called tumor suppressor miRs. Many onco-miRNA (miR-21, miR-31, miR-99-3p, miR-128a, miR-128b, miR-139, miR-141, miR-146a, miR-146b-3p, miR-146b-5p, miR-155, miR-181a, miR-181b, miR-187, miR-191, miR-200a, miR-200b, miR-200c, miR-220, miR-221, miR-222, miR-222-5p, miR-224, miR-375, miR-551b) or suppressor miRNA (let-7, miR-1, miR-26a-1, miR-30, miR-30c, miR-138, miR-199, miR-219, miR-292, miR-300. and miR-345) have been reported in thyroid cancer [17–21]. Further, each subtype of thyroid cancer may have its own miRNA profile. miR-182 and miR-183 are reported more in FVPTC compared to PTC; upregulation of miR-21 and miR-22 and downregulation of miR-204, miR-144-3p, miR-15a-5p, miR-20a-5p, miR-32-5p miR-142-5p, miR-143-3p, and miR-20b-5p are associated with aggressive behavior in classic variant PTC [19–22], and upregulation of miR-222-3p has been reported to discriminate FVPTC from NIFTP [19]. Germline mutations of

let-7e, miR-181b, miR-135a, miR-15b, miR-320, and miR-484 have been associated with familial PTC [17].

Therapeutic targeting of miRNA dysregulation is under investigation. Molecules designed to mimic miRNA to replace downregulated tumor suppressor miRNAs that are combined with hydrogels, liposomes, minicells, nanoparticles, synthetic polymers, or viral carriers for better delivery are under investigation [18].

Abnormalities in lncRNA, longer counterparts of short ncRNA, likely also play a role in thyroid carcinogenesis. lncRNA are involved in gene modulation including regulation of gene expression, chromatin modification, protein complex assembly, splicing, and translation. Both tumor-suppressive lncRNAs (*NAMA*, *PTCSC 1/2/3*, *MEG3*, *LING00271*, *CASC2*, *PANDAR*) and oncogenic lncRNA (*MALAT1*, *HOTAIR*, *BANCR*, *PVT1*, *FAL1*) have been reported [16].

Currently, however, few diagnostic products and no therapeutic products, utilizing ncRNA have entered clinical use. One thyroid diagnostic utilizing miRNA was briefly available [23], while one remains on the market in the United States and is discussed below.

Genomics of Thyroid Cancer

Papillary Thyroid Cancer

Genomic analysis of papillary thyroid cancer (PTC) showed unique features which set this cancer apart from other common adult cancers [22, 24]. The most striking finding was a low mutational burden of 0.41/Mb, approximately four genomic changes across the entire exome. This is much lower than cancers of the breast (median 1.2/Mb), colon (3.2/Mb), and lung (8–10/Mb) and rather similar to pediatric cancers (0.1–0.3/Mb) [25, 26]. The other finding was the apparent mutual exclusivity of driver mutations. The mutation that "drives" the carcinogenesis or, more specifically, a mutation which confers a selective cell growth advantage is called a *driver mutation*. Coexistence of canonically mutually exclusive alterations is seen [27], but their rarity suggests little, or no, selective growth advantage once the pathway is activated by a strong driver.

In PTC, the most frequent driver mutation was $BRAF^{V600E}$ (60%), followed by *RAS* (14%). It is important for the reader to recognize that the PTC of this study is not representative of those typically found among cytologically indeterminate nodules where $BRAF^{V600E}$ mutation is much less common. In one study, $BRAF^{V600E}$ was present in just 11% of PTC variants found in Bethesda III/IV cytology groups [28]. Still, The Cancer Genome Atlas (TCGA) project illuminated important lessons. Both *BRAF* and *RAS* encode proteins involved in the mitogen-activated protein kinase (MAPK) pathway (Fig. 2.8), a crucial cellular transduction pathway to regulate cellular proliferation and cell cycle. *BRAF* was relatively rare in follicular variant PTC (FVPTC) (7%), whereas it was by far the most common mutation

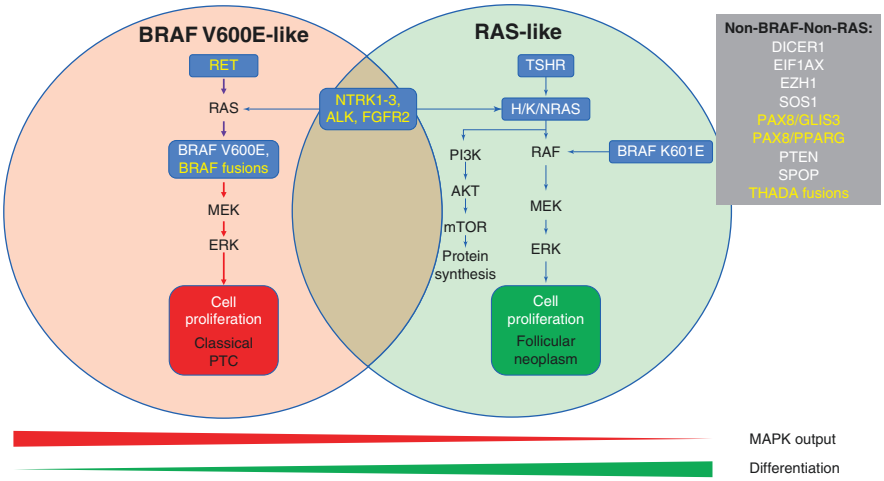

Fig. 2.8 MAPK pathway. Genomic variants and fusions categorized according to published literature [22, 39]. Variants and fusions in white and yellow letters, respectively. *RET* fusions are *BRAF*^{V600E}-like. *RET* point mutations are typically medullary thyroid carcinoma. Colors of the arrows convey the magnitude of pathway signaling (e.g., *BRAF*^{V600E} variant (red) > *RET* fusion (purple) > *RAS* variants (blue)), which may account for different tumor phenotypes and behaviors. (Figure adapted from published literature [22, 88])

in classic variant PTC (71%) [22]. *RAS* was the most frequent driver mutation in FVPTC (35%). Given this clear distinction, TCGA categorized PTC to *BRAF*^{V600E}-like and *RAS*-like cancers (Fig. 2.8). Tumors driven by *BRAF*^{V600E} do not respond to the negative feedback from *ERK* to *RAF*, resulting in high MAPK signaling [29]. Conversely, tumors driven by *RAS* and *RTK* fusions signal via *RAF* dimers to respond to *ERK* feedback, resulting in lower MAPK signaling.

This differential signaling results in phenotypic differences. For example, expression of genes responsible for iodine uptake and metabolism are greatly reduced in *BRAF*^{V600E}-like cancers [30]. In contrast, the *RAS*-like cancers' expression of these genes is largely preserved [22]. TCGA also found that *RAS*-like PTC was well differentiated, carried a lower risk of recurrence, and was more associated with follicular structure compared to *BRAF*^{V600E}-like counterparts. TCGA focused on tumor-initiating events; hence, most were low-risk PTC (poorly and undifferentiated carcinomas were excluded). Since *RAS* variants and many other variants and fusions found in PTC (and follicular thyroid cancer (FTC)) are also found among nonmalignant neoplasms, it seems obvious that additional events/factors beyond just these genomic alterations are needed to form thyroid cancer.

Understanding those additional events is an active area of research. Genomic studies of poorly differentiated thyroid cancer (PDTC) and anaplastic thyroid cancer (ATC) have followed [31–34], which showed *BRAF*^{V600E} and *RAS* remaining as the most common driver mutations. However, the overall mutation burden was higher, with additional mutations in genes such as *TERT*, *TP53*, *MED12*, *RBM10*,

CDKN2A, and *CDKN2B*. In a mouse model, the addition of a *TP53* mutation to $BRAF^{V600E}$-altered PTC dramatically transformed indolent PTC to PDTC/ATC [35]. This suggests that subsequent specific genetic alterations in addition to original driver event(s) may cause a transformation of indolent differentiated thyroid cancer to a more aggressive cancer.

Follicular Adenoma and Follicular Thyroid Cancer

Despite having a worse prognosis than PTC [36–38], cytological and genomic characteristics of FTC overlap significantly with benign follicular adenoma (FA), which poses a unique challenge. At the molecular level, *RAS* mutation (*NRAS*, *KRAS*, and *HRAS*) and *PAX8/PPARγ* translocation are both frequently seen in FTC, up to 50% of cases [39]. However, they are also seen in FA, albeit less frequently (2%–25%) [39–41], making these unreliable molecular markers to differentiate between FTC and FA by themselves. Indeed, among nodules with Bethesda III/IV cytopathology, the positive predictive values (PPVs) of *PAX8/PPARγ*, *HRASQ61*, *BRAFK601E*, and *NRASQ61R* were 55%, 45%, 42%, and 38%, respectively [42]. These findings suggest that these genomic events most likely contribute to an early phase of carcinogenesis; however, additional genomic alterations are required for an adenoma to carcinoma transformation to occur [39, 40, 43, 44].

Hürthle Cell Cancer

The Hürthle cell derives from a thyroid follicular cell, but its appearance is quite distinct; it is larger, contains abundant mitochondria, and has prominent nucleoli (Fig. 2.5) [45–49]. Hürthle cells are seen in benign thyroid conditions, such as Hashimoto thyroiditis and benign nodular goiter. However, neoplasms composed of >75% Hürthle cells are labeled as Hürthle cell adenomas (HCA) or Hürthle cell carcinomas (HCC) [46]. Similar to FTC, HCC cannot be distinguished from HCA cytologically because the distinction is made histologically based on capsular or vascular invasion. HCC was once believed to be a variant of FTC [49]. However, given its unique clinical and cytological profiles, the World Health Organization recategorized Hürthle cell carcinomas as a separate entity from FTC in 2017 [49, 50]. Unlike FTC, HCC is typically resistant to radioactive iodine therapy and has a higher possibility of cervical lymph node metastasis and intense F-18 fluoro-2-deoxyglucose positron emission tomography avidity. Its prognosis is worse than FTC, particularly when distant metastasis develops [38]. Recent genomic analyses reveal unique genomic alterations of HCC, characterized by mitochondrial DNA alterations and widespread losses of heterozygosity and chromosomes [3, 45, 46, 48]. Loss of heterozygosity is also found among HCA [3]. Incorporation of these findings into molecular diagnostic tests has improved diagnostic performance of Hürthle cell lesions [3, 40, 51].

Medullary Thyroid Cancer

Medullary thyroid cancer (MTC) is derived from the calcitonin-secreting parafollicular cell. Twenty-five percent of MTC occurs as a part of multiple endocrine neoplasia type 2 (MEN2), whereas others occur sporadically. Genomic analysis of both sporadic and hereditary MTC showed three main driver mutations, *RET*, *HRAS*, and *KRAS* [52–54], which are canonically mutually exclusive and comprise approximately 75% of MTC across multiple studies, with point mutations in *RET* being the most common (50%–60%). Current practice guidelines recommend that patients with presumed sporadic MTC undergo germline *RET* mutation testing [55].

Genomics in Cytologically Indeterminate Results

Due to the intermediate risk of malignancy (10%–25%) [56], the demand grew for better diagnostic testing in Bethesda III/IV nodules and led to substantial genomic research in this population to differentiate between benign and malignant lesions. The most common mutations (60%) seen in this group are categorized as non-$BRAF^{V600E}$-like (*NRAS*, *HRAS*, *KRAS*, *EIF1AX*, *BRAFK601E*, *PPARγ* fusion, *DICER1*), followed by a group without a clear driver mutation; these include copy number alteration, insertions/deletions (indels), and gene expression alteration [40, 41]. Frustratingly, like their cytologically "indeterminate" results, these mutations are also insufficient to differentiate between benign from malignant lesions, as they occur in both benign and malignant lesions [40]. $BRAF^{V600E}$-like mutations ($BRAF^{V600E}$, *BRAF*, and *RET* fusions), on the other hand, are known (or suspected) to be highly specific for cancer (>95%) and when present convey with near certainty the presence of thyroid cancer [42, 57]. However, these are uncommon in the cytologically indeterminate population [58]. Overall, each individual observed mutation has low sensitivity, and most have modest specificity to diagnose cancer. Hence, multiple genomic alterations need to be analyzed to achieve overall high sensitivity, but the addition of the many alterations with modest specificity leads to a diminished overall panel specificity that by itself cannot rule in cancer with high accuracy. In the next section, we discuss the most common molecular tests commercially available.

Commercially Available Thyroid Nodule Molecular Tests

Afirma® Gene Expression Classifier and Afirma Gene Sequencing Classifier

The Afirma Gene Expression Classifier (GEC) was launched in 2011 (Veracyte, Inc., South San Francisco, CA) to avoid diagnostic surgery in Bethesda III/IV nodules by serving as a thyroid cancer "rule-out" molecular diagnostic test. It designated

indeterminate nodules as molecularly either "benign" or "suspicious" by algorithmic utilization of the mRNA gene expression patterns defined via a microarray of 167 genes. Afirma GEC was clinically validated in a prospective, double-blinded, multicenter study [59] which included 265 Bethesda III/V nodules. Among Bethesda III/IV nodules, sensitivity, specificity, PPV, and negative predictive value (NPV) were 90%, 52%, 37%, and 94%, respectively, with a cancer prevalence of 24%. All cases had a blinded histopathological reference. Multiple post-validation studies followed, demonstrating high sensitivity and NPV in various settings (Table 2.1, Fig. 2.9) [60–64]. While it served as a good "rule-out test," its relatively low specificity precluded its use as a "rule-in test," most pronounced among Hürthle cell lesions [65].

As genomic understandings, methodologies, and machine-learning tools advanced, a second-generation Afirma test was developed [3, 45, 46, 48]. The Afirma Gene Sequencing Classifier (GSC) was developed in pursuit of improved specificity. GSC utilizes an RNA-sequencing platform, and the core benign versus suspicious classifier includes 10,196 genes [3, 51]. GSC classification workflow begins with measurement of the quantity and quality of RNA (Fig. 2.10). Satisfactory samples are then tested with four upstream "malignancy classifiers" (parathyroid tissue, MTC, *BRAF*^{V600E} variant, and *RET/PTC1* and three fusions). If these classifiers are negative and the specimen passes the follicular content classifier, then the core classifier categorizes samples as GSC benign or suspicious (Fig. 2.10) [3, 51]. The core classifier is integrated with the Hürthle cell index and Hürthle neoplasm index. These classifiers automatically detect Hürthle cytology samples and allow those that are nonneoplastic to be processed by the core classifier with an adjusted threshold so that more of these low-risk samples receive a benign result [3].

Afirma GSC was clinically validated using the same blinded, prospectively accrued, multi-institutional cohort of thyroid FNA samples on which the GEC was validated [51, 59]. Direct comparison to the GEC showed improved specificity (68% vs 52%) and PPV (47% vs 37%). The GSC was introduced for commercial use in 2017. Since then, four independent post-validation studies have been published (Table 2.2, Fig. 2.11) [66–69] which show improvement in the benign call rate and improved specificity and PPV, especially in nodules with HC changes.

The Afirma Xpression Atlas (XA) is an additional test that provides more genomic information among Afirma GSC suspicious nodules, Bethesda V/VI nodules, and thyroid cancer metastases [70]. XA utilizes RNA sequencing to report 761 RNA variants and 130 RNA fusions from 511 genes to better understand the biopsied nodule or metastasis. Among GSC suspicious nodules, a negative result does not negate the cancer risk of a GSC suspicious nodule [70]. Yoo et al. reported that malignancies that were negative for variants or fusions via comprehensive RNA sequencing tended to be unifocal, lacked extrathyroidal extension and local and distant metastases, and were free of disease [39]. However, these findings were not entirely consistent with those of the 126 TCGA PTCs (out of 496) that lacked a driver mutation or fusion [22]. Thus, further investigation of this topic is warranted.

Table 2.1 Summary of Afirma GEC studies

Author	Year	Bethesda	Total	Benign (% of total)	Surgery *N* (% of total)	Cancer[a] *N* (prevalence)	SE*N* (%)	SPE (%)	PPV[b] (%)	NPV (%)
San Martin [69]	2019	III	103	47 (46%)	85 (48%)	16 (18%)	94	64	37	98
		IV	75	26 (35%)		17 (26%)	100	54	44	100
Endo [68]	2019	III	228	115 (50%)	117 (51%)	28 (12%)	93	61	27	98
		IV	115	50 (40%)	63 (50%)	26 (21%)	96	61	45	98
Angell [67]	2019	III, IV	486	233 (48%)	249 (51%)	77 (16%)	97	61	34	99
Harrell [66]	2018	III, IV	481	200 (42%)	270 (56%)	139 (29%)	86	67	57	91
Azizi [90]	2018	III, IV	156	92 (59%)	76 (49%)	31 (20%)	90	74	48	97
Deaver [91]	2018	III	118	61 (52%)	48 (41%)	17 (14%)	100	69	39	100
		IV	41	12 (29%)	27 (66%)	6 (15%)	100	38	23	100
Hang [92]	2017	III	293	141 (48%)	133 (45%)	47 (16%)	100	68	42	100
		IV	78	28 (36%)	42 (54%)	10 (13%)	90	47	23	96
Harrison (repeat FNA) [93]	2017	III, IV	105	52 (50%)	45 (43%)	14 (13%)	100	65	33	100
Kay-Rivest (St. John's cohort)[c] [95]	2017	III	21	12 (57%)	9 (43%)	2 (10%)	100	63	22	100
		IV	42	17 (41%)	24 (57%)	15 (36%)	100	63	63	100
Kay-Rivest (Montreal cohort)[c] [94, 95]	2017	III	84	54 (64%)	25 (30%)	9 (11%)	100	77	36	100
		IV	25	6 (24%)	19 (76%)	12 (48%)	100	46	63	100
Samulski[c] [94, 96]	2016	III	159	99 (62%)	56 (35%)	20 (13%)	95	77	40	99
		IV	118	45 (38%)	65 (55%)	24 (20%)	92	55	39	96
Wu [97]	2016	III	217	102 (47%)	107 (49%)	55 (25%)	93	73	58	96
		IV	28	11 (39%)	21 (75%)	8 (29%)	100	58	50	100
Abeykoon [98]	2016	III, IV	34	17 (50%)	16 (47%)	12 (35%)	100	81	75	100
Dhingra [99]	2016	III, IV	24	12 (50%)	12 (50%)	7 (29%)	100	71	58	100

(continued)

Table 2.1 (continued)

Author	Year	Bethesda	Total	Benign (% of total)	Surgery *N* (% of total)	Cancer[a] *N* (prevalence)	SE*N* (%)	SPE (%)	PPV[b] (%)	NPV (%)
Villabona [100] (first FNA series only)	2016	III	48	21 (44%)	21 (44%)	14 (29%)	100	75	67	100
Sacks [101]	2016	III, IV	120	48 (40%)	58 (48%)	18 (15%)	100	57	33	100
Al-Qurayshi [102]	2016	III	114	48 (42%)	84 (74%)	36 (32%)	78	64	55	83
		IV	40	10 (25%)	28 (70%)	14 (35%)	79	33	44	70
Witt [103]	2016	III	17	7 (41%)	10 (59%)	3 (18%)	100	50	30	100
		IV	12	7 (58%)	5 (42%)	3 (25%)	100	78	60	100
Zhu [104]	2015	III, IV	44	23 (52%)	10 (23%)	6 (14%)	100	85	60	100
Celik [105]	2015	III	8	2 (25%)	6 (75%)	4 (50%)	100	50	67	100
		IV	26	9 (35%)	14 (54%)	6 (23%)	100	60	50	100
Marti MSK series [106]	2015	III, IV	94	24 (26%)	44 (47%)	24 (26%)	100	57	57	100
Marti MSBI series [106]	2015	III, IV	71	37 (52%)	26 (37%)	3 (9%)	100	67	14	100
McIver [107]	2014	III	5	0 (0%)	5 (100%)	1 (20%)	100	0	20	Null
		IV	55	16 (29%)	31 (56%)	5 (9%)	80	40	15	94
Lastra [107]	2014	III	68	45 (66%)	18 (27%)	11 (16%)	100	0	61	Null
		IV	64	25 (39%)	32 (50%)	11 (17%)	100	10	37	100
Alexander (University of Cincinnati only) [60]	2014	III	16	7 (44%)	6 (38%)	2 (13%)	100	64	33	100
		IV	12	10 (83%)	2 (17%)	2 (17%)	100	100	100	100
Alexander[d] [59]	2012	III	129	55 (43%)	129 (100%)	31 (24%)	90	53	38	95
		IV	81	32 (40%)	81 (100%)	20 (25%)	90	49	37	94

[a]Noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP) is included with malignancy for all calculations. Smaller studies with overlapping data were excluded

[b]For all calculations, unoperated molecularly benign nodules are considered true benign and unoperated suspicious nodules are excluded

[c]Data derived from Valderrabano et al. [94]

[d]Clinical validation study [59]

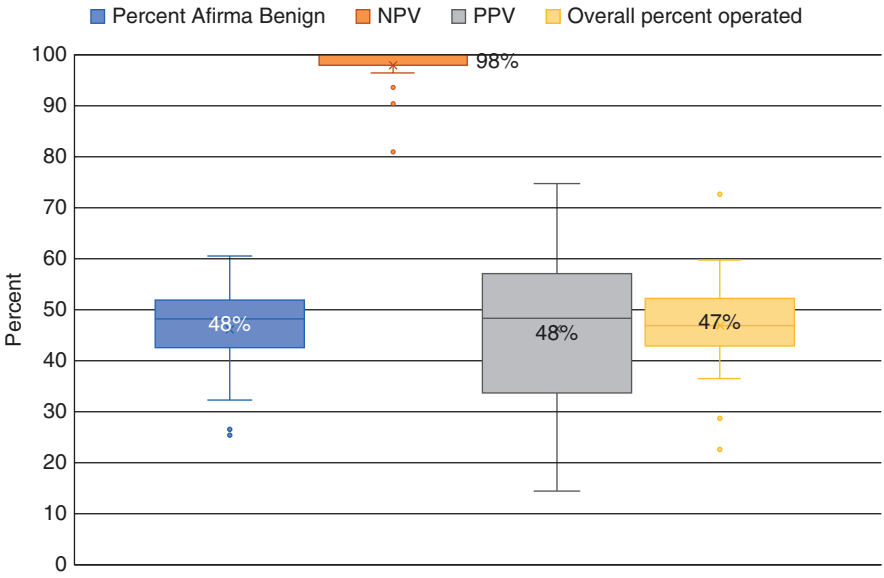

Fig. 2.9 Box and whisker plot of Afirma GEC combined Bethesda III/IV performance from 25 independent series from Table 2.1. Unweighted averages are shown. The boxes enclose the interquartile range (IQR). *Whiskers* extend up from the top of the *boxes* to the largest data element that is less than or equal to 1.5 times the IQR above the top of the box and down from the bottom of the *box* to the smallest data element that is less than or equal to 1.5 times the IQR below the bottom of the box

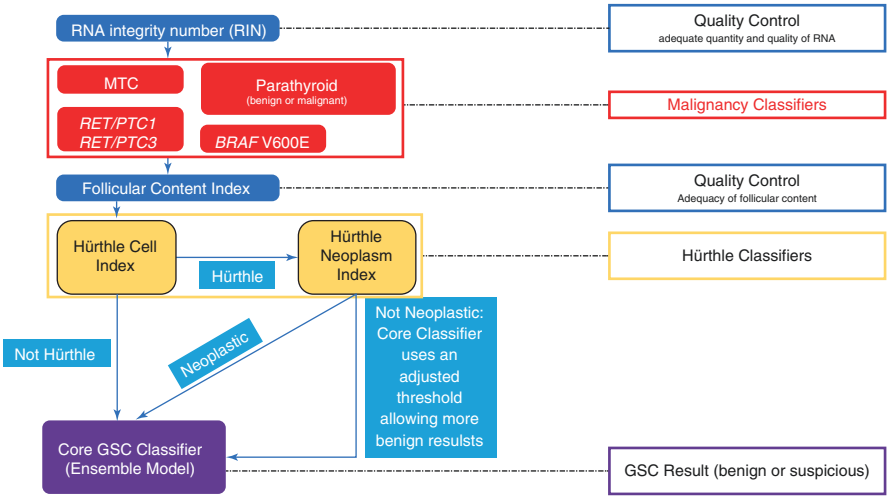

Fig. 2.10 Afirma GSC schematic. (Adapted from published literature [3, 51])

Table 2.2 Summary of Afirma GSC studies[a]

Author	Year	Bethesda	Total	Benign (% of total)	Surgery *N* (% of total)	Cancer[b] *N* (prevalence)	SEN (%)	SPE (%)	PPV (%)	NPV (%)
San Martin [69]	2019	III	76	58 (76%)	42 (35%)	14 (19%)	86	95	80	97
		IV	45	24 (54%)		18 (42%)	94	92	90	96
Endo [68]	2019	III	124	100 (81%)	17 (14%)	8 (6%)	100	94	57	100
		IV	40	25 (63%)	12 (30%)	7 (18%)	100	86	64	100
Angell [67]	2019	III, IV	114	75 (66%)	37 (32%)	17 (15%)	94	82	50	99
Harrell [66]	2018	III, IV	139	85 (61%)	45 (32%)	29 (21%)	97	90	76	99
Patel[c] [51]	2018	III	114	63 (55%)	114 (100%)	28 (25%)	93	71	51	97
		IV	76	40 (53%)	76 (100%)	17 (22%)	90	49	37	94

[a]For all calculations, unoperated molecularly benign nodules are considered true benign and unoperated suspicious nodules are excluded
[b]Noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP) is included with malignancy for all calculations
[c]Clinical validation study

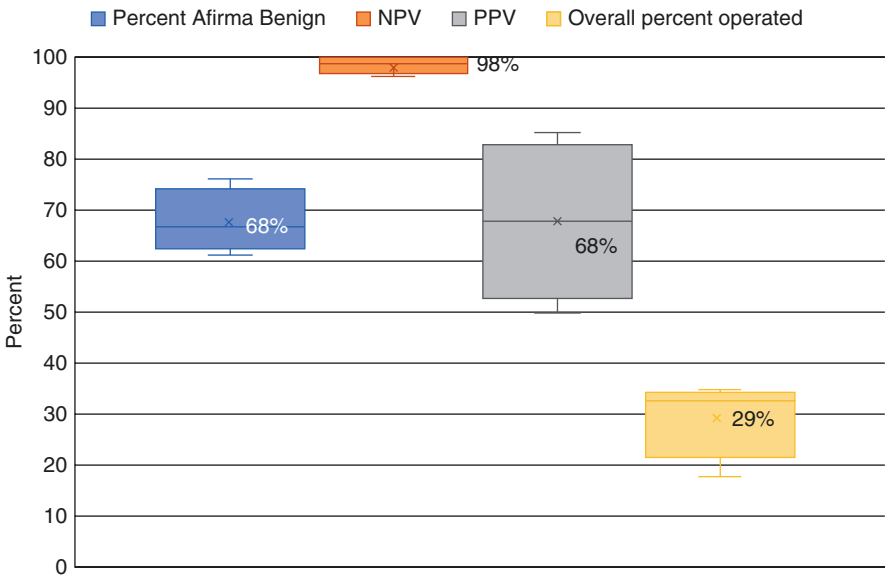

Fig. 2.11 Plot of Afirma GSC combined Bethesda III/IV performance from three independent series from Table 2.2. Unweighted average values of each metric are shown

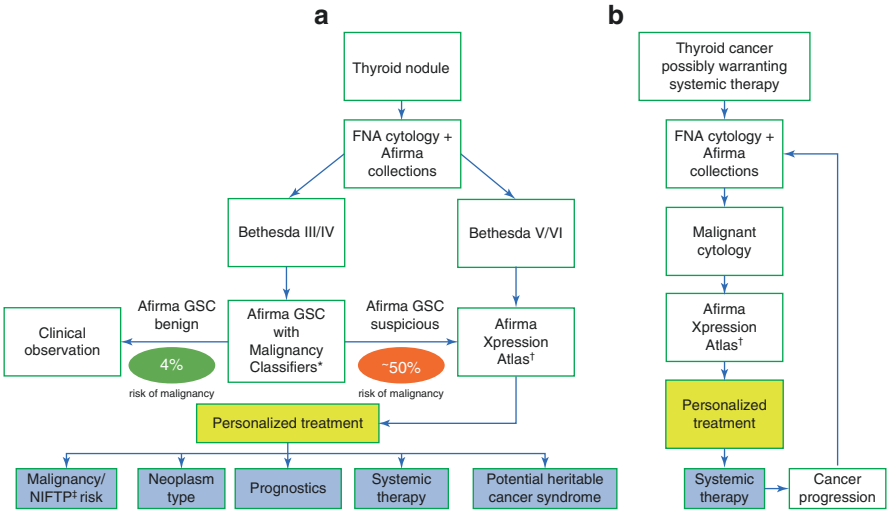

Fig. 2.12 The role of Afirma Xpression Atlas among thyroid nodules (panel A) and known thyroid cancer metastases (panel B). *Malignancy classifiers report every sample as positive or negative for the MTC classifier, *BRAF*^{V600E} classifier, parathyroid classifier, and *CCDC6/RET* (*RET/PTC1*)+*NCOA4/RET* (*RET/PTC3*) fusions. †Malignancy classifiers are included with the Xpression Atlas. ‡Noninvasive follicular thyroid neoplasms with papillary-like nuclear features. (Adapted from Ali et al. [89])

Alternatively, positive findings on XA may denote alteration-specific PPV information, likely neoplasm type, pathway signaling classification, and the potential presence of a genomic alteration targeted by an FDA-approved or investigational therapy, and may identify an alteration that should prompt consideration of genetic counseling and germline testing for the possibility of an inherited syndrome (MEN2, Cowden, familial adenomatous polyposis/Gardner, DICER1, hereditary breast and ovarian cancer, and others) (Fig. 2.12). This additional knowledge may help tailor the management such as the extent of the surgery and potentially whether to pursue additional treatments such as radioactive iodine therapy. Of note, testing for TERT promoter variants is currently not available, although they are relatively rare in Bethesda III/IV nodules. These concepts are more fully discussed below in the "Molecular Diagnostics Beyond Bethesda III/IV Nodules" section.

ThyroSeq

ThyroSeq is a multigene panel test that was developed at the University of Pittsburgh Medical Center. Its first large validation study (seven-gene panel, recently referred to as ThyroSeq v0), published in 2011, was a single-institution retrospective analysis and correlation of 1056 consecutive FNA samples of thyroid nodules with

indeterminate cytology from 762 patients at the University of Pittsburgh Medical Center [44]. After assessment of adequacy, final molecular analysis was performed on 967 FNA samples from 729 patients, and histological correlation was available for 513 FNA samples in 479 patients who underwent surgery. The gene alterations tested were *BRAF*^{V600E}, *NRAS* codon 61, *HRAS* codon 61, and *KRAS* codons 12/13 point mutations, as well as *RET/PTC1*, *RET/PTC3*, and *PAX8/PPARγ* rearrangements. Overall, 24% of nodules with indeterminate cytology were malignant on final pathology (14% in the AUS/FLUS (Bethesda III) category, 27% in the FN/SFN (Bethesda IV) category, and 54% in the SMC (Bethesda V) category). If any mutation was identified on the multigene panel, the overall risk of malignancy (PPV) was 89% (88% in the AUS/FLUS (Bethesda III) category, 87% in the FN/SFN (Bethesda IV) category, and 95% in the SMC (Bethesda V) category), with a sensitivity of 57%–68%, specificity of 96%–99%, and an NPV of 72%–94% depending on the specific indeterminate cytology subcategory. Criticisms of this study include its single-center design and establishment of the histopathological diagnosis without blinding to molecular results.

Since initially introduced, ThyroSeq molecular testing platforms and versions have been evolving. ThyroSeq v2 clinical validation and independent clinical experience studies have been published (Table 2.3 and Fig. 2.13). ThyroSeq is currently commercially available from CBLPath (Rye Brook, NY), with its multigene

Table 2.3 Summary of ThyroSeq V2 studies[a]

Author	Year	Bethesda	Total	Negative (% of total)	Surgery *N* (% of total)	Cancer[b] *N* (prevalence)	SEN (%)	SPE (%)	PPV (%)	NPV (%)
Taye [108]	2018	III, IV	153	51 (67%)	60 (39%)	12 (8%)	83	79	27	98
Livhits [109]	2018	III, IV	76	61 (80%)	23 (30%)	8 (11%)	100	91	57	100
Valderrabano [110]	2017	III	104	82 (79%)	52 (50%)	7 (7%)	43	86	19	95
		IV	86	63 (73%)	50 (58%)	13 (15%)	85	91	65	97
Nikiforov[c] [111, 112]	2015 2014	III	95	69 (73)	69 (100%)	22 (23%)	91	92	77	97
		IV	143	101 (71%)	143 (100%)	39 (27%)	90	93	83	96

[a]For all calculations, unoperated molecularly benign nodules are considered true benign and unoperated suspicious nodules are excluded

[b]Noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP) is included with malignancy for all calculations

[c]Clinical validation study

panel consisting of 112 genes tested by next-generation sequencing (ThyroSeq v3, Table 2.4). Its clinical validation study, published in 2018, was a prospective double-blinded multicenter study of 1031 FNA biopsies in 782 patients at ten

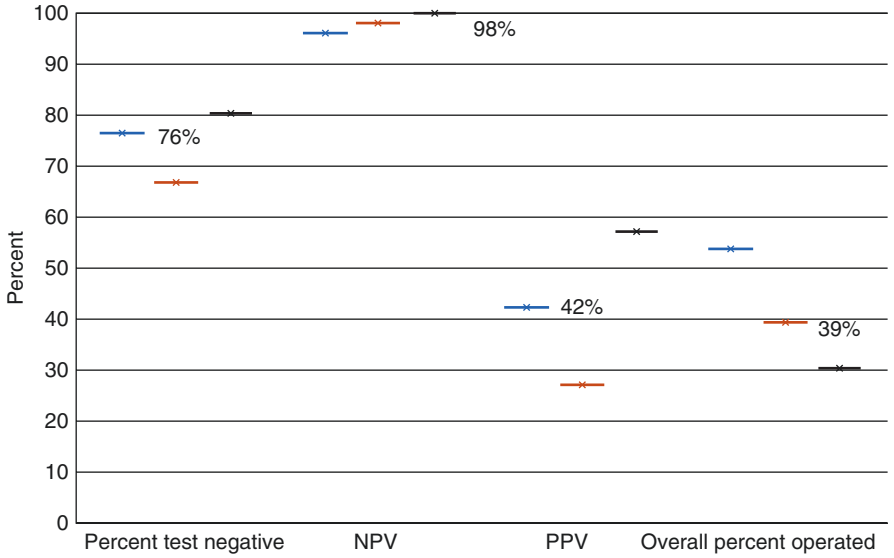

Fig. 2.13 Plot of ThyroSeq v2 combined Bethesda III/IV performance from three independent series from Table 2.3. Unweighted average values of each metric are shown

Table 2.4 Summary of ThyroSeq v3 studies

Author	Year	Bethesda	Total	Negative (% of total)	Surgery *N* (% of total)	Cancer[a] *N* (prevalence)	SEN (%)	SPE (%)	PPV (%)	NPV (%)
Nikiforova [113]	2018	III, IV	158	83 (53%)	158 (100%)	70 (44%)	98	82	83	99
Steward[b] [40]	2018	III	154	104 (68%)	154 (100%)	35 (23%)	91	85	64	97
		IV	93	46 (49%)	93 (100%)	33 (35%)	97	75	68	98

[a]Noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP) is included with malignancy for all calculations
[b]Clinical validation study

medical centers, nine in the United States and one in Singapore [40]. After exclusions and assessment of adequacy, final molecular analysis was performed on 257 nodules with indeterminate cytology in 232 patients. Histological correlation was available for all of these nodules. Eleven nodules were diagnosed as NIFTP, and the malignancies and NIFTPs were analyzed together when the performance of the 112 gene panel was reported. Of 257 nodules with indeterminate cytology who underwent both molecular testing and surgery, 76 (30%) were either cancer or NIFTP (35/154 (23%) in the AUS/FLUS (Bethesda III) category, 33/93 (35%) in the FN/SFN (Bethesda IV) category, and 8/10 (80%) in the SMC (Bethesda V) category). The primary outcome of the study was the ability to distinguish cancer or NIFTP from benign nodules in the Bethesda III and IV categories. Molecular testing was positive in 39% of samples and negative in 61% of samples. With a cancer/NIFTP prevalence in the combined Bethesda III and IV categories of 28%, the ThyroSeq v3 multigene classifier had a sensitivity of 94%, specificity of 82%, PPV of 66%, and NPV of 97%. With a cancer/NIFTP prevalence in the entire cohort (including the ten patients in the Bethesda V category) of 30%, the ThyroSeq v3 multigene classifier had a sensitivity of 93%, specificity of 81%, PPV of 68%, and NPV of 97%. The five (3%) false negatives were T1 or T2 PTCs ($n = 4$) or minimally invasive follicular thyroid cancer ($n = 1$). The authors were also able to identify the following genes with alterations as associated with a 100% risk of neoplastic disease: *TERT*, *TP53*, and $BRAF^{V600E}$ mutations and *NTRK3*, *RET*, and *BRAF* fusions. Interestingly, of 34 test-positive nodules that were histologically benign (23 (67%) adenomas and 11 (32%) hyperplastic nodules), 32 (94%) exhibited one or more clonal alteration in a large proportion of cells in the nodule, indicating a neoplastic (and not hyperplastic) process. These findings suggest a potential value of combining the molecular information with histological interpretation. One of the strengths of this study, in addition to its prospective multicenter design, is that all of the histopathology was done centrally and neither the cytologists nor the pathologists were aware of the molecular testing results. It is noted that prevalence of malignancy was overall higher in ThyroSeq studies compared to Afirma, which positively influences its PPVs. Criticisms of this study include that two of the ten centers contributed most of the samples and the cancer/NIFTP prevalence was 43% or higher among four centers, raising questions of sample selection bias and generalizability of the results to other practice settings.

Recently, a clinical experience study of ThyroSeq restricted to indeterminate nodules with Hürthle cell changes was published. This included 188 Hürthle cell lesions with 33 surgical follow-ups [71]. All cases were tested with ThyroSeq v2, and selected cases were additionally tested with ThyroSeq v3. Of these, 115 (61%) had negative test results, and five were operated and were benign on surgical pathology. Seventy-three had positive test results and 28 were operated. Among operated cases, PPV and NPV on Bethesda III nodules were 55% and 100%, respectively. For Bethesda IV nodules, PPV was lower at 36%, with NPV 100%.

Table 2.5 Summary of ThyGenX/ThyraMIR

Author	Year	Bethesda	Total	Negative (% of total)	Surgery *N* (% of total)	Cancer *N* (prevalence)	SEN (%)	SPE (%)	PPV (%)	NPV (%)
Labourier[a] [74]	2015	III, IV	109	67 (61%)	109 (100%)	35 (32%)	89	85	74	94

[a]A multiplex reverse transcription PCR platform (miR*Inform*) was used. This test was replaced for commercial use by testing with a next-generation sequencing platform under the same ThyGenX name. Clinical validation of that test or its replacement, ThyGeNEXT, is unpublished

ThyGeNEXT+ThyraMIR

ThyGeNEXT+ThyraMIR, offered by Interpace Diagnostics (Pittsburgh, PA), is a unique combination testing of gene mutation/fusion panel using next-generation exome sequencing and a microRNA classifier. Although certain miRNAs are preferably expressed in thyroid cancer [22, 72], its low sensitivity made it insufficient to serve as a diagnostic test by itself [73]. ThyGeNEXT includes mutational analysis of ten genes and 38 gene fusions. ThyraMIR (miRNA classifier) testing is reflexively triggered when ThyGeNEXT is negative for genetic alterations or if a mutation with lower specificity for cancer is detected. ThyraMIR stratifies samples as either low or high risk for cancer based on expression patterns of ten miRNAs. Recommended sample acquisition is one dedicated FNA pass collected in a nucleic acid preservative. No clinical validation or independent clinical experience studies have been published. An earlier seven-gene mutation panel acquired from Asuragen Inc. (Austin, TX) and using multiplex PCR and liquid bead array cytometry platforms to report among 17 genomic alterations together with ThyraMIR was clinically validated in a multi-institutional cross-sectional study [74] including 109 Bethesda III/IV nodules with histopathological reference (Table 2.5). Histological labels were assigned locally and blinded to the ThyraMIR result but unblinded to the seven-gene panel result. Sensitivity, specificity, PPV, and NPV of 89%, 85%, 74%, and 94% were reported with relatively high cancer prevalence of 32%. Among the 35 cancers, 31 were identified as positive by the test (24 by a genomic variant or fusion and 20 by ThyraMIR). While this validation study named this testing combination ThyGenX/ThyraMIR, Interpace subsequently used the same ThyGenX name for a new next-generation sequencing test that added the PIK3CA gene and added genomic findings from among >100 alterations. No clinical validation of this test version has been published. One clinical experience study reported that among a cohort with a 14% risk of cancer, 92% of patients with negative results by ThyGenX and ThyraMIR were cancer-free at 2 years after FNA by Kaplan-Meier analysis. They also studied an alternative reporting system that also counted patients as negative when ThyGenX demonstrated a “weak” driver mutation and

ThyraMIR was negative. Using this approach, 87% of patients with a negative test result were cancer-free at 2 years after FNA by Kaplan-Meier analysis. Compared to the reported baseline prevalence of cancer, the cancer reduction reported in this study appears quite modest: lower rates of cancer-free status may reasonably be expected among commonly encountered cohorts with higher cancer prevalence.

How to Use Molecular Testing Results to Guide Surgery

Before the advent of molecular testing, most patients with indeterminate cytology were recommended to undergo surgical biopsy (resection) for definitive diagnosis, and the majority of these nodules turned out to be benign. Surgical biopsy usually involves thyroid lobectomy, with its attendant risks of anesthesia, bleeding potentially requiring reoperation, recurrent laryngeal nerve injury, damage to or inadvertent removal of parathyroid glands, and impact on postoperative thyroid hormone levels. With the development of commercially available molecular testing platforms, diagnostic thyroid lobectomy can be avoided in most patients with negative molecular testing.

With the reclassification of the encapsulated follicular variant of papillary thyroid cancer (PTC) as noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP) in 2016 [7], both the risk of malignancy of each indeterminate cytology subcategory [6] and the performance of molecular testing platforms have changed. This impact is diminished, however, if a goal of molecular testing is to identify and surgically remove NIFTP. Before ordering any molecular testing for an FNA biopsy with indeterminate cytology, it is important to discuss with the patient the risk of malignancy for each indeterminate subcategory, as well as the risk of malignancy associated with negative molecular testing (which is not zero).

Some patients prefer a definitive diagnosis of their thyroid nodule, in which case surgery should be discussed with the patient and molecular testing not ordered. Other circumstances in which patients should probably proceed directly to surgery are thyroid nodules in a patient with any other indication for thyroidectomy (e.g., nodules causing compressive symptoms, nodules in the setting of Graves' disease in a patient who desires surgical therapy for hyperthyroidism, nodules in the setting of goiter with tracheal compression or substernal extension), thyroid nodules with a high suspicion sonographic pattern (e.g., hypoechoic with microcalcifications, taller than wide, irregular margins, extrathyroidal extension, or interrupted rim calcification) whose risk of malignancy is >70%–90% [1], or thyroid nodules whose FNA biopsy is in the SMC (Bethesda V) subcategory [6]. Still, in each of these scenarios, an argument can be made to consider molecular testing if the result would change the extent of surgery or preoperative evaluation, such as the molecular identification of MTC.

Most physicians and patients would agree that surgery is indicated for a thyroid nodule with a positive molecular testing result, i.e., a suspicious result using the Afirma Gene Sequencing Classifier (GSC) or a specific gene alteration detected on a multigene panel test that conveys a significant risk of cancer. The risk of malignancy is approximately 50% for a suspicious result using the Afirma GSC (with a sensitivity of 91% and specificity of 68%) [51], and the risk of malignancy depends on the specific gene alteration identified on the multigene panel test of ThyroSeq v3, ThyGeNEXT, or the Afirma Xpression Atlas.

Molecular testing of cytologically indeterminate thyroid nodules seems to have the most usefulness for FNA biopsies in the AUS/FLUS (Bethesda III) and FN/SFN (Bethesda IV) categories, since 70%–94% of nodules in the AUS/FLUS (Bethesda III) and 60%–90% of nodules in the FN/SFN (Bethesda IV) categories on FNA biopsy will turn out to be benign on histopathology, depending on whether or not NIFTP is considered a malignancy [6]. Thus, there is potential to avoid diagnostic surgery in a high percentage of patients whose FNA biopsy result is in one of these categories.

Some clinicians propose that molecular testing may also be useful in patients whose FNA biopsy is in the SMC (Bethesda V) category, as knowledge of a specific gene mutation may change the planned extent of surgery. For example, because the *BRAF*^{V600E} mutation has been reported to be associated with extrathyroidal extension, lymph node metastasis, and advanced clinical stage [75, 76], some clinicians may use this information to recommend more extensive initial surgery. For example, a total thyroidectomy with central neck dissection might be advised in a patient with a small PTC who could otherwise be treated with thyroid lobectomy. However, because data analyzing long-term outcomes of the use of molecular testing information to inform such clinical decisions are lacking, caution should be used if deciding to use molecular testing results for this purpose.

Molecular Diagnostics Beyond Bethesda III/IV Nodules

One may argue that current thyroid cancer guidelines are not precise, or helpful, for a large fraction of thyroid cancer patients regarding initial thyroid surgery or postoperative radioiodine usage. Genomic assessment of thyroid nodules with Bethesda V/VI cytology and thyroid cancer metastases or unresectable local disease may be increasingly important toward tailoring care to the individual patient (e.g., precision medicine).

Nearly 90% of patients with papillary thyroid cancer are stage I by the eighth edition of the AJCC/UICC Staging System and have a 5-year disease-specific survival of 99.7% [77]. Yet, for patients with thyroid cancer >1 cm and <4 cm without extrathyroidal extension and without clinical evidence of any lymph node metastases

(all stage I if histologically confirmed), the 2015 American Thyroid Association Management Guideline [1] permits either hemithyroidectomy or total thyroidectomy (Recommendation 35). Similarly, postoperative radioiodine "may be considered" or is "considered" for nearly all patients (Table 14 of the guideline). Thus, potentially, the same patient may be advised to undergo a hemithyroidectomy alone or, alternatively, total thyroidectomy plus radioiodine ablation. A more informed approach to treatment decisions is desired.

Recent studies have begun to associate selected variants and fusions with *BRAF*^{V600E}-like versus *RAS*-like categories, iodine metabolism, neoplasm histology, risk of lymph node metastasis, risk of recurrence, and risk of mortality [22, 39]. TCGA studied PTC, including the classic, follicular variant and tall cell variants [22]. Yoo et al. investigated minimally invasive FTC, follicular adenoma, PTC, and follicular variant of PTC [39]. They reported three gene expression profiles: *BRAF*^{V600E}-like, *RAS*-like, and non-*BRAF*-non-*RAS* (NBNR) (Fig. 2.8). These molecular subtypes were correlated with differences in copy number variation, cell proliferation, differentiation, intracellular signaling, and metabolism. *RAS*-like genomic alterations included the *H/K/NRAS* variants and the *STRN-ALK* and *FGFR2-KIAA1598* fusions. Overlap between the *BRAF*^{V600E}-like and *RAS*-like groups was seen for *NTRK3* fusions and *CCDC6-RET*. Similar overlap/borderline separation was seen in the TCGA analysis for fusions of *NTRK3*, *MET*, and *LTK* [22]. TCGA identified all *BRAF* variants other than V600E as RAS-like, including the *BRAF*^{K601E} variant. Discrepant from the positioning by Yoo et al. [39], TCGA suggested a more borderline/overlap positioning for *NTRK1* and *ALK* fusions, more *RAS*-like positioning for all *FDFR2* fusions, and more *BRAF*^{V600E}-like positioning for all RET fusions. The Yoo et al. [39] NBNR group was associated with *DICER1*, *EIF1AX*, *IDH1*, *PTEN*, *PAX8/PPARγ*, *PAX8-GLIS3*, *THADA-LOC100505678*, *EZH1*, *SOS1*, *IDH1*, and *SPOP*. Higher frequency of lymph node metastases and extrathyroidal extension were seen in the *BRAF*^{V600E}-like group, while less was observed in the *RAS*-like or NBNR groups. Notable was that NBNR group lacked any lymph node metastases. These data suggest the need for clinical trials that combine clinical and radiological factors with genomic data to derive more precision-medicine-based treatment recommendations. At a minimum, these data seem to suggest that tumors clinically confined to the thyroid and preoperatively identified to harbor *RAS*-like or NBNR genomic alterations may be more strongly considered for more conservative intervention such as lobectomy alone. For such clinical trials or patient management, it may be prudent to exclude genomic alternations from the *RAS*-like or NBNR groupings alterations where current evidence suggests their possible clustering or overlap with *BRAF*^{V600E}-like group. These excluded variants would include fusions of *BRAF*, *RET*, *NTRK1/3*, *MET*, *LTK*, and *ALK*.

Across oncology, it has been suggested that each cancer can be genomically subtyped and that the downstream gene expression profile predicts the tumor's cellular morphology, clinical presentation, and prognosis. These signaling pathways present an opportunity for the development of effective targeted therapies to improve disease-specific survival. This approach has led to many preclinical studies and

ultimately to a marked increase of clinical trials for patients with refractory thyroid cancer that match the tumor's genomic alteration with pharmaceuticals that act upon the targeted pathway.

While not all successful, several of these trials have demonstrated impressive preliminary clinical activity. Such studies have led to the FDA approval for refractory thyroid cancer of the combination of dabrafenib plus trametinib for *BRAF*^{V600E}-mutated anaplastic thyroid cancer [78], pembrolizumab for microsatellite instability-high or mismatch repair deficient thyroid cancer [79], and larotrectinib and entrectinib for thyroid cancer harboring an *NTRK* fusion [80, 81]. More genome alteration-centered clinical trials and FDA approvals are expected. Pembrolizumab and larotrectinib mark the first two FDA approvals of oncologic therapeutics that were genome-specific and tumor type agnostic, a complete reversal of the historical approach. Thus, it is expected that genomic profiling of thyroid cancers and their metastases will assume greater importance. This is likely to include tumor profiling over multiple time points, including at initial diagnosis, when systemic therapy is being considered, and upon disease progression while under active treatment. Clinicians are likely to soon describe thyroid cancer patients by their genomic profile in the same way they currently describe them by their histological diagnosis. Profiling from a large genomic panel has merits because many of the targetable alterations are rare, and profiling via an FNA specimen would be less invasive and more cost-effective compared to repeated profiling from surgical specimens.

Future Directions

Guiding Initial Management and Subsequent Follow-Up Strategies in Malignant Cases

Understanding the molecular characteristics of an indeterminate nodule may not only improve initial decisions of whether to undergo a surgery but also guide management and subsequent follow-up strategies.

Development of a classifier to recognize ATA low-risk cancers/nodules preoperatively with high confidence would empower the surgeon to perform just a hemithyroidectomy and reduce excessive surgery and radioactive iodine therapy. It is likely that such a classifier would outperform classification according to *BRAF*^{V600E}-like, *RAS*-like, and NBNR signaling pathways.

RAS-positive cancers have less frequency of lymph node metastasis which indicate these entities may require less frequent follow-up neck ultrasound (US) compared to *BRAF*^{V600E}-like or *RET/PTC* cases [82]. These patients may be able to be transferred to a survivorship clinic once achieving no evidence of disease status.

A molecular classifier to predict a response to radioactive iodine could be helpful. Adjuvant radioiodine treatment when the tumor is unlikely to be affected exposes the patient to unnecessary radiation, anxiety, cost, and inconvenience. In addition, approximately 10%–15% of high-risk thyroid cancer patients develop resistance to radioiodine [83, 84]. Non-iodine avidity may be inferred by utilizing information of the *BRAF*^{V600E}*-RAS* score proposed in TCGA and associated with regulation of genes involved in expression of sodium-iodine cotransporter such as *SLC5A5*, *SLC5A8*, *DIO1*, *DIO2*, *DUOX1*, and *DUOX2* [22]. This knowledge may aid clinicians to determine whether to proceed with radioiodine treatment.

Prognostics of Benign Nodules

Eleven percent of benign nodules (defined either by sonographic features or cytology results) will eventually increase in size in relatively iodine-deficient areas during 8.5 years of follow-up [85]. Another study done in the United States showed that 17% benign nodules eventually underwent thyroidectomy after 8 years of follow-up, mainly due to compressive symptoms [86]. Larger thyroid size is associated with higher risk of surgical complication in benign thyroid disease [87]; hence, predicting benign nodules unlikely to significantly grow versus those likely to grow may improve the clinical decision-making and follow-up. Work would be required to validate such a test and its cost-effectiveness.

Summary

Molecular analysis of thyroid nodules has advanced rapidly from single variant tests to large molecular panels and classifiers. Rapid development is likely to continue. Initial questions of benignity versus malignancy are extending to additional questions regarding prognostics to inform decisions of clinical observation and the extent of surgical resection. Concurrently, drug development of selective agents with reduced side effects is occurring at a rapid pace. We anticipate that knowing the patient's molecular status will soon be equally relevant as knowing their histological diagnosis and stage. Obtaining molecular information with minimally invasive approaches is likely to be better tolerated and more cost-effective. To date, tissue sampling has demonstrated greater diagnostic yields over measurement of circulating tumor DNA, including among anaplastic carcinomas in which higher rates of circulating tumor DNA are detected. These rapid advancements in medical genomics have created a significant knowledge gap where most practicing clinicians are not fluent with this knowledge, including thyroidologists. Patients and physicians

will likely benefit by ongoing educational efforts and carefully constructed patient test reports to distill the complexities of genomic information into summaries that facilitate appropriate decision-making. These efforts will be needed to fully realize the potential benefits of personalized medicine on thyroid nodule and cancer care.

Conflicts of Interest RTK is an employee and equity owner of Veracyte, Inc. whose products include the Afirma® Gene Sequencing Classifier and Xpression Atlas. The views expressed here may not represent those of Veracyte, Inc. ME, NM, and DE do not have a conflict of interest.

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Chapter 3
Active Surveillance for Thyroid Cancer

Caitlin B. Iorio and David C. Shonka Jr

Introduction

Incidence of Thyroid Cancer

Thyroid nodules are widely prevalent in the general population. Palpable nodules are present in approximately 5% of women and 1% of men living in iodine-sufficient areas of the world [1, 2]. They are more frequently found in women and the elderly, and often, their diagnosis can be attributed to the use of high-resolution ultrasound (US) which can detect thyroid nodules in 16%–68% of randomly selected individuals [3, 4]. The primary clinical significance of thyroid nodules lies in their risk of harboring thyroid cancer, which occurs in 7%–15% of nodules, depending on age, sex, history of radiation exposure, family history, and other clinical factors [5, 6]. Papillary and follicular thyroid cancer is grouped under the umbrella term differentiated thyroid cancer (DTC), which comprises the majority (>90%) of all thyroid cancers [7].

The incidence of thyroid cancer was stable until the early 1990s when it nearly tripled from 4.9 per 100,000 in 1975 to 15.8 per 100,000 in 2016. However, over this period of time, thyroid cancer mortality remained stable [8]. This surge has been attributed to an increase in the diagnosis of papillary thyroid cancer (PTC), particularly smaller lesions. In the 1980s, 25% of newly diagnosed thyroid cancers were less than 1 cm, whereas 39% of new thyroid cancers were less than 1 cm in 2008 [8]. This trend has been observed internationally as well. One study

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https://doi.org/10.1007/978-3-030-73951-5_3

demonstrated that the incidence of non-incidental papillary thyroid microcarcinoma (PTMC) (i.e., PTMC diagnosed prior to thyroid surgery and not just incidentally identified on final pathology) increased from 17% to 34% between 2008 and 2016 [9]. The increase in the diagnosis of thyroid cancers smaller than 1 cm is believed to be largely due to the increasing use of neck US and other imaging modalities and a lower threshold for fine-needle aspiration biopsy [10].

It is possible to detect thyroid nodules that are as small as 3 mm with high-resolution neck US, and lesions of this size can be further evaluated with US-guided fine-needle aspiration biopsy (FNAB) in expert hands [11]. This ability has allowed for the diagnosis of a large reservoir of subclinical papillary cancer. This was famously documented in a Finnish study in which autopsy specimens demonstrated a 35.6% prevalence of occult papillary carcinoma in patients who had died of non-thyroid causes [12]. Based on these findings, it can be surmised that operations can likely be avoided in patients with small, incidentally discovered PTMC as they have an exceptional prognosis.

Despite the increased incidence of thyroid cancer, the mortality rate associated with these cancers has remained stable. This is not unexpected given that most of this increase is due to identification of many low-risk PTCs. The prognosis for these small lesions is excellent. However, although mortality has remained the same, the number of thyroid surgeries has increased, and this has significant implications for patients and the healthcare system at large.

Cost of Thyroid Cancer Care

The increasing incidence in thyroid cancer has had increasing clinical and economic consequences. Aschebrook-Kilfoy et al. gathered incidence and funding data from the National Cancer Institute's (NCI) Surveillance, Epidemiology, and End Results Database (SEER) and the Office of Budget and Finance and estimate that the lifetime cost for a hypothetical cohort of patients with thyroid cancer is $34,723 per patient. The lifetime cost of patients without metastasis was $33,463 per patient, whereas the cost of those with metastasis was $58,660 per patient. The economic impact of thyroid cancer diagnosed in 2010 was approximately $1.4 billion and increased to more than $2.38 billion (or $3.1 billion unadjusted) for the 2019 cohort. Utilizing these data, the sustained increase in thyroid cancer incidence will be responsible for an additional cost of $4.5 billion dollars (or $7.5 billion undiscounted) over the next 10 years [13]. Increasing incidence is resulting in a greater prevalence of thyroid cancer survivors. The majority of these patients will live full lives after their diagnosis, but they are likely to undergo long-term surveillance or management of postoperative consequences such as hypothyroidism or hypoparathyroidism which will ultimately lead to further economic burden on the healthcare system.

Complications of Thyroid Surgery

There are risks inherent in thyroidectomy such as hypocalcemia due to hypoparathyroidism, vocal fold paralysis, and hypothyroidism. One large cross-sectional study of 62,722 procedures showed a 20% risk of any complication with total thyroidectomy and an 11% risk of complication with thyroid lobectomy. While the complication rate was lower for high-volume surgeons (>99 procedures per year), this cohort of surgeons performed only approximately 5% of all of the procedures. Even in the hands of high-volume surgeons, total thyroidectomy was associated with a significantly higher risk of complications compared to thyroid lobectomy [14]. Given the exceptional prognosis for PTC and PTMC in particular, when permanent complications do occur as a result of surgery, the affected patient is likely to deal with the ramifications of the complication for a protracted period of time.

Reducing Thyroid Cancer Diagnosis

As detailed above, the overdiagnosis of PTMC and resulting overtreatment are a significant problem for the healthcare system at large and for individual patients. One study evaluating the incidence of thyroid cancer in 12 countries estimates that at least 470,000 women and 90,000 men were overdiagnosed with thyroid cancer in these countries over two decades [15]. One approach to potentially address this problem is to avoid making the diagnosis of PTMC. Recommendation 8 of the 2015 American Thyroid Association guidelines for adult patients with thyroid nodules and DTC states that thyroid nodules without accompanying lymphadenopathy should not undergo fine-needle aspiration until ≥1 cm diameter, even when high-suspicion ultrasound features are present [16]. There are no studies to date evaluating the impact of this recommendation on the incidence of PTMC diagnosed in the United States or internationally. While the hope is that the frequency of the diagnosis will decrease, it likely will continue to represent a significant clinical quandary for the foreseeable future.

Active Surveillance

Active surveillance (AS) is another management paradigm, which has gained traction recently, aimed at reducing the burden of thyroid cancer management. AS of DTC has been proposed as an alternative option to surgery for patients with favorable thyroid malignancies, particularly those with PTMC. This approach relies on our understanding of the frequency of subclinical PTMC and the relatively indolent nature of PTC more generally.

Patients with small papillary thyroid carcinomas are currently being maintained under AS instead of being submitted to immediate surgery in certain centers in Japan and other Asian countries [11, 17–20]. In these centers, if a PTC is 10 mm or less, the patient is presented two management options: observation alone or surgical treatment. The criteria needed to recommend AS usually include the following: (i) adult individual, (ii) tumor ≤1 cm and not adjacent to the trachea or recurrent laryngeal nerve, (iii) cytology not suggestive of an aggressive subtype, and (iv) absence of lymph node (LN) involvement and extrathyroidal extension (ETE) based on US assessment [11, 17–20]. Thus, the safe selection of candidates for AS largely depends on cytology and US excluding tumors with a higher risk of progression or complications. Patients who choose observation undergo serial US once or twice a year [20, 21].

AS was adopted as a management modality in Japan in 2011 in the guidelines issued by the Japan Association of Endocrine Surgeons (JAES)/Japanese Society of Thyroid Surgery (JSTS) [22]. Similarly, Recommendation 12 of the 2015 ATA guidelines also supports AS as a treatment option for PTMC [16]. These recommendations are based on a substantial amount of clinical data supporting the utility of AS as a management strategy.

Clinical Data

Ito, Miyauchi, and colleagues from Kuma Hospital in Kobe, Japan, first published the results of AS for 162 patients with PTMC in 2003 [20]. Additional patients were added to the original observation group, and the data from 340 patients undergoing observation was subsequently published by Ito et al. in 2010 [21]. The most recent study by Ito includes 1235 patients who underwent observation with at least 18 months of follow-up [11]. In this study, 58 (4.6%) of 1235 patients had confirmed enlargement in the size of the PTMC (defined as an increase in size of the cancerous nodule by 3 mm or more), 19 (1.5%) developed biopsy-proven lymph node metastasis, and 43 (3.5%) showed progression to clinical disease (defined as PTMC measuring 12 mm or greater) during the follow-up period. Of the 1235 patients enrolled in observation, 191 (16%) patients ultimately underwent surgery for various reasons such as tumor enlargement or development of lymph node metastasis. These patients were followed for an average of 75 months after surgery. Only one of these patients developed a recurrence. This patient underwent lobectomy and developed a small PTC in the residual thyroid lobe which was under observation at the time of the paper's publication. None of the patients in the study died of thyroid cancer or were found to have distant metastasis. The low recurrence rate in the patients who ultimately underwent surgery and the absence of any disease-specific deaths demonstrate that AS is a reasonable management option and that a delay in surgical intervention after a period of observation is unlikely to affect disease-specific survival or recurrence rate in PTMC.

In a separate center in Japan, Sugitani and colleagues published the results of a prospective clinical trial of observation for asymptomatic PTMC [23]. In this study, 230 patients underwent observation of PTMC (some with multiple tumors) for a mean duration of 5 years. All patients were followed with US, and an increase or decrease in size of the PTMC was defined as a change of 3 mm or more. In this study, 90% of tumors showed no change, 7% increased in size, and 3% decreased in size. During the follow-up period, no patients developed distant metastasis or extrathyroidal extension, but three patients (1%) developed nodal metastasis. Ultimately, 16 patients (7%) underwent surgery [23].

More recent studies from centers outside of Japan have supported the findings reported by Ito and Sugitani. A study from the Asan Medical Center in Seoul, Korea, by Kwon and colleagues retrospectively evaluated 192 patients with PTMC under active surveillance for >1 year [18]. A change in maximal tumor diameter was defined as ≥3 mm difference in any dimension compared to previous measurement, and a change in tumor volume was defined as a >50% difference in volume compared to volume at initial diagnosis. During the median follow-up of 30.1 months, there was an increase in tumor volume in 14% and an increase in maximal diameter in 2%. There was no significant change in tumor size in 69% and a decrease in size in 17%. Only one patient (0.5%) developed clinically evident lymph node metastasis. Ultimately, 13% underwent delayed thyroid surgery during the study period [18]. A separate multicenter cohort study in Korea evaluated 370 patients with PTMC retrospectively and used the same definitions of tumor maximal diameter and volume change [24]. This study found that 3.5% of patients had an increase in maximal diameter of the tumor during the median 32.5-month follow-up period. The cumulative incidence of increase in volume rose over time with 6.9% demonstrating an increase in tumor volume at 2 years and 36.2% at 5 years. Five patients (8.6%) developed lymph node metastasis. Of the 370 patients, 58 (5.7%) underwent delayed thyroid surgery [24].

The first study reporting on a trial of AS in the United States was published by Tuttle and colleagues in 2017 [19]. This study enrolled 291 patients with low-risk PTC measuring up to 1.5 cm without evidence of extrathyroidal extension, invasion of local structures, or nodal/distant metastasis. US examinations were performed every 6 months for 2 years and then annually with a median follow-up of 25 months. Tumor growth of ≥3 mm diameter occurred in 11 of 291 patients (3.8%) – 2.5% at 2 years and 12.1% at 5 years. Some of the patients (6.7%) were noted to have a decrease in tumor volume during the observation period. As was noted in the Japanese and Korean studies, tumor growth was more likely to occur in younger patients in this cohort [11, 19, 23, 24]. Subsequent studies from Brazil and Columbia have reported similar positive outcomes [25, 26].

A meta-analysis that included several of the trials summarized above showed pooled proportions of size enlargement and development of lymph node metastasis at 5 years of 5.3% and 1.6%, respectively [27]. A different meta-analysis showed a pooled proportion of tumor growth during AS of 4.4% and development of metastatic nodal disease of 1.0% [28]. This second meta-analysis also showed no difference in tumor growth, development of cervical nodal metastasis, incidence of

Table 3.1 Summary of several trials of AS for PTC

First author	Year	Country	Design	Number of patients	Tumor diameter increase (≥3 mm)	Surgery performed after AS	Follow-up
Sugitani (45)	2014	Japan	Prospective	322	6%	8.7%	78 m (mean)
Ito [11]	2014	Japan	Retrospective	1235	4.6%	16%	75 m (mean)
Kwon [22]	2017	Korea	Retrospective	192	2%	13%	30.1 m (median)
Tuttle [23]	2017	The United States	Prospective	291	3.8%	3.4%	25 m (median)
Oda [37]	2016	Japan	Prospective	1179	2.3%	8%	47 m (median)
Oh [28]	2018	Korea	Retrospective	370	3.5%	5.7%	32.5 m (median)
Sanabria [30]	2018	Columbia	Prospective	57	3.5%	9%	13.3 m (median)
Rosario [29]	2019	Brazil	Prospective	77	1.4%	3.9%	30 m (median)
Sakai [33]	2019	Japan	Prospective	360	8%	NR	87.6 m (mean)

thyroid surgery, or disease recurrence between AS for patients with PTMC compared to those with PTCs up to 15 mm. Several recent studies also appear to support the safety of AS for these larger cancers [28, 29]. Table 3.1 summarizes a number of trials of AS for PTC.

Adoption/Implementation of Active Surveillance

There are several potential barriers to implementation and acceptance of AS as a management option for DTC. One major obstacle that is often overlooked is the dedicated team and resources required to safely initiate and maintain an AS program. Success with AS is highly dependent on appropriate patient selection, extensive patient counseling, and unerring follow-up. This requires a dedicated team of skilled cytopathologists, radiologists, endocrinologists, and surgeons. The groups at Memorial Sloan Kettering Cancer Center and Kuma Hospital have defined some of the nuances of patient selection for AS and the practical considerations involved in implementing an AS program [30]. To date, all of the studies that have shown such promising results with AS have been performed at major, academic medical centers with highly skilled and dedicated multidisciplinary teams. This team is responsible for careful selection of patients with tumors that are appropriate for AS, accurate

diagnosis of DTC without concerning pathologic features, consistent performance and interpretation of ultrasound examinations, and safe and thorough performance of rescue surgery when indicated. This level of care can currently only be provided at a select number of institutions.

A second major barrier to the widespread adoption of AS is its acceptance as a management option by physicians and patients. Despite strong clinical evidence and endorsement by the JSTS and ATA of AS, it is not widely offered or implemented in current practice. One reason for this may be that AS is not even understood as a possible management strategy by many physicians or patients. In a study of patient experience with AS in Kuma Hospital, 77% of patients had not heard of AS as an option for PTMC until after diagnosis [31]. However, even when awareness exists, adoption of AS can take many years [32].

Importantly, patients may be reluctant to undergo observation after a confirmed diagnosis of DTC. Of 2153 patients with low-risk PTMC diagnosed at Kuma Hospital between 2005 and 2013, 54.8% chose AS, and 45.2% chose immediate surgery [33]. In a study by Sugitani and colleagues, 244 patients with asymptomatic PTMC were offered observation, and 14 (6%) declined [23]. Convincing patients with larger tumors to enroll in AS appears to be even more challenging. In a study comparing patients with PTMC and T1b PTC, 11% of patients with PTMC chose immediate surgery, while 84% (331 of 392 patients) with T1b tumors chose immediate surgery [29].

A further challenge to AS is its long-term tenability for patients. It appears that some patients become unhappy with AS as a management option and choose to proceed with surgical treatment after a period of time. An additional 2% of the patients in the study by Sugitani elected to undergo surgery during the observation period due to a change in personal preference, despite the absence of a size increase or the development of nodal metastasis [23]. Indeed, a meta-analysis of several studies showed that 3.4%–32% of patients enrolled in AS trials ultimately undergo thyroid surgery and 32%–66% of these patients have surgery for reasons other than size enlargement or development of lymph node metastasis [27]. It does appear, however, that for a significant percentage of patients undergoing AS, their anxiety about their disease decreases with time. A study by Davies et al. sought to measure the patient experience with AS for thyroid cancer [31]. When patients on AS were asked how much they worried about their thyroid cancer, 14% responded “not at all,” 42% “rarely,” and 37% “sometimes or more.”

Cost-Effectiveness

The rising incidence of DTC has led to an increasing economic burden for healthcare systems. One potential advantage of AS over immediate surgery for DTC is a potential reduction in the cost of care. At this point, there are limited data regarding the difference in costs between immediate surgery and AS. However, the 10-year cost of active surveillance versus immediate surgery appears to be lower, at least in

a Japanese setting. In 2017, Oda et al. reported that the 10-year total cost of immediate surgery for PTMC was 4.1 times the 10-year total cost of AS [34].

It may be that patient age is a crucial consideration for the cost-effectiveness of AS. A study from Australian setting showed that the cost of surgical management of PTMC was equivalent to the estimated cost of 16.2 years of AS [35]. The authors concluded therefore that surgical management may be more cost-effective for younger patients with PTMC. Miyauchi and colleagues estimated the lifetime probability of progression of PTMC during AS, if diagnosed in the 20s as 60%, 30s as 37%, 40s as 27%, 50s as 15%, 60s as 10%, and 70s as 3.5% [36–40]. Given this data, from a pure cost-saving perspective, it is possible that AS may be more appropriate for older patients diagnosed with DTC [37].

Future Directions

One of the primary concerns with AS is the possibility that a patient may have an aggressive version of PTMC and that this could progress during the surveillance period. If extrathyroidal extension or metastatic nodal disease develops, rescue surgery might require a more extensive operation than would have been performed if the patient had been treated with immediate surgery. In the case of nodal disease, it is impossible to know if these nodes already harbored metastatic PTC at the time of initial diagnosis and would have become clinically evident even if immediate surgery was performed. But, at least in theory, it is likely that immediate surgery would likely prevent some patients from developing metastatic disease. While unusual, patients with PTMC occasionally present with significant nodal metastasis and distant metastatic disease. A SEER Database study of 18,445 cases of PTMC identified 49 thyroid-cancer-related deaths and a 99.5% disease-specific survival, meaning that 0.5% of patients died of PTMC [38]. Presumably all advanced PTC started as a PTMC at some point. Opponents of AS for PTMC point out that current technological limitations prevent identification of patients with these more aggressive tumors.

Molecular profiling of tumors has arisen as a possible means of identification of more aggressive thyroid cancers. One study evaluated the implications of the $BRAF^{V600E}$ status on the recurrence rate of PTMC. In this study, the recurrence rate was 1.3% in patients with BRAF-mutation-negative PTMC versus 4.3% in patients with BRAF-mutation-positive PTMC [39]. Unfortunately, the positive predictive value of the BRAF mutation in isolation is relatively low which limits the applicability of this tumor marker for directing patient care. Coexistence of multiple mutations may give additional information about tumor potential for aggressive behavior. The combination of BRAF and TERT mutations is associated with more high-risk clinicopathologic characteristics of PTC, higher recurrence rate, and worse disease-free survival than either mutation alone [40]. It is anticipated that further studies of molecular profiling in combination with a better understanding of host immune response to tumors will ultimately further facilitate improved stratification of individual patients with PTMC.

Conclusions

The incidence of thyroid cancer is increasing internationally predominately due to the overdiagnosis of small differentiated thyroid cancers that have an excellent prognosis. Surgical treatment of thyroid cancer can result in hardship for individual patients, especially those who develop complications related to thyroid surgery. Additionally, the rising incidence of thyroid cancer is associated with significant economic burden to the healthcare system at large. AS has emerged as an alternative to surgical management. The available clinical data indicate low risk of disease progression during AS and excellent results of rescue surgery if deemed necessary. Further studies are necessary to define the cost implications of AS compared to immediate surgery, to determine the psychological impact of AS on patients, and to more clearly identify those patients at highest risk for disease progression who are unlikely to benefit from AS as a long-term management option.

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Chapter 4
Hemithyroidectomy for Differentiated Thyroid Cancer

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Historical Context and Overview

The prevailing management paradigm over the last 30 years for well-differentiated thyroid cancer required a total thyroidectomy, often with some degree of compartment-oriented lymph node dissection, and radioactive iodine (RAI) therapy for all but the most low-risk differentiated thyroid cancers [1]. More recently, the dramatic increase in detecting and diagnosing very low-risk differentiated thyroid cancers has led to a renewed interest in a risk-adapted, therapeutic, and follow-up management approach. Since the one-size-fits-all routine use of RAI therapy is now becoming a much less common therapeutic approach for patients with low- to intermediate-risk differentiated thyroid cancer, the standard use of a total thyroidectomy simply to facilitate RAI therapy and follow-up management must be re-evaluated. In response to these important issues and based on the re-evaluation of large retrospective datasets, the American Thyroid Association (ATA) and the National Comprehensive Cancer Network (NCCN) guidelines currently recommend a much more risk-adapted approach for determining the extent of the initial surgical resection and the use of RAI therapy [2, 3].

According to the most recent editions of both the ATA and NCCN guidelines, oncologically acceptable initial treatment options include either a hemithyroidectomy (thyroid lobectomy ± isthmusectomy) or a total thyroidectomy for patients with intrathyroidal, differentiated thyroid cancer tumors that are less than 4 cm in maximal diameter without evidence of associated gross extrathyroidal extension,

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M. C. Singer, D. J. Terris (eds.), *Innovations in Modern Endocrine Surgery*,
https://doi.org/10.1007/978-3-030-73951-5_4

vascular invasion, or macroscopic nodal disease [2, 3]. While the guidelines have referred to a lobectomy as the less aggressive surgical option, we also endorse an isthmusectomy as a reasonable procedure, using the same decision-making processes that would be used for a lobectomy, for small, differentiated thyroid cancer tumors that are confined to the isthmus [4]. Both guidelines also stress the importance of integrating patient preferences and values with the philosophy of the disease management team arriving at the optimal, initial surgical management approach for an individual patient.

In this chapter, we briefly overview the current literature that pertains to important oncologic outcomes in patients with differentiated thyroid cancer who were treated with either hemithyroidectomy or total thyroidectomy. We describe how to classify patients—based on intra-operative and postoperative findings—as ideal, appropriate, or inappropriate candidates for initial minimalistic management options. This classification takes into account three critical domains: tumor and imaging results, patient characteristics and preferences, and disease management team characteristics and treatment philosophy (Fig. 4.1) [5, 6]. We also review our approach to dynamic risk stratification and follow-up management, as well as surveillance recommendations in patients who are selected for hemithyroidectomy [7, 8].

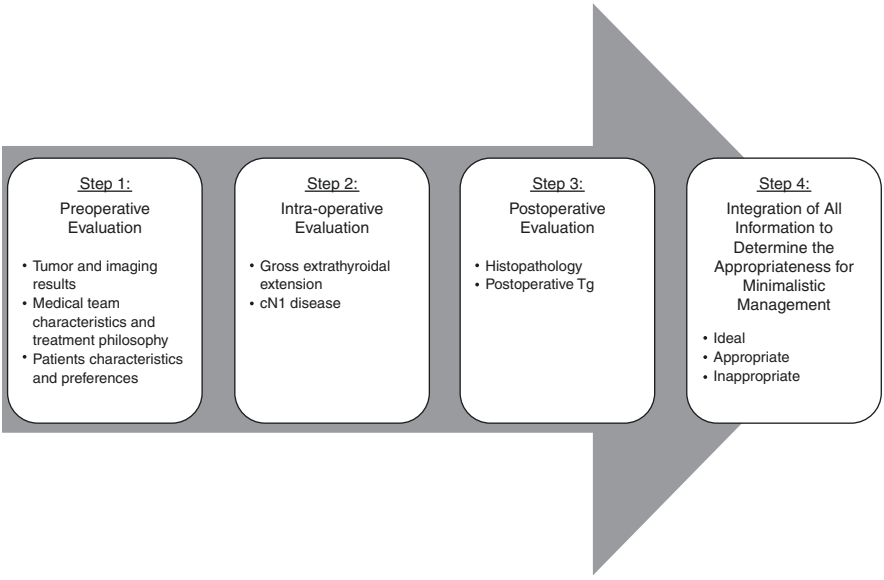

Fig. 4.1 Selecting patients for a minimalistic initial surgical management approach using a thyroid lobectomy or isthmusectomy without cervical lymph node dissection or radioactive iodine treatment. *Abbreviations*: cN1 clinical staging of N1 disease, Tg thyroglobulin

Oncologic Outcomes Following Hemithyroidectomy

For many years, total thyroidectomy was recommended for all patients with differentiated thyroid cancer, except for those with very low-risk disease, primarily due to the prevailing opinion that routine use of RAI therapy facilitated follow-up management, often decreased the risk of recurrence, and in some patients improved disease-specific mortality. The 2009 ATA guidelines relied heavily on an analysis of 52,173 patients with papillary thyroid cancer from the National Cancer Database (NCDB) who were diagnosed between 1985 and 1998 (43,227 total thyroidectomy vs. 8946 lobectomy), which demonstrated that patients who had total thyroidectomy as opposed to lobectomy had a slightly higher 10-year relative overall survival (98.4% vs. 97.1%, respectively; $P < 0.05$) and a slightly lower 10-year recurrence rate (7.7% vs. 9.8%, respectively; $P < 0.05$) [9]. Statistically significant differences in survival and recurrence, based on the extent of initial surgery, were seen for all tumor sizes greater than 1 cm in maximal diameter.

A re-evaluation of this issue examined 29,522 patients from the NCDB (26,371 total thyroidectomy vs. 3151 lobectomy) and 13,510 patients from the Surveillance, Epidemiology, and End Results (SEER) database (12,131 total thyroidectomy vs. 1379 lobectomy); when statistical analysis is adjusted for important patient and clinical characteristics, such as age and tumor size, there were no differences in survival for those who received a total thyroidectomy versus a lobectomy [10]. These findings are consistent with the lack of survival benefit associated with total thyroidectomy in properly selected patients as reported by Haigh et al. (4612 total thyroidectomy vs. 820 lobectomy) [11]; Barney et al. (12,598 total thyroidectomy vs. 3266 lobectomy) [12]; Mendelsohn et al. (16,760 total thyroidectomy vs. 5964 lobectomy) [13]; Nixon et al. (528 total thyroidectomy vs. 361 lobectomy) [14]; Matsuzu et al. (1088 lobectomy) [15]; Liu et al. (341 total thyroidectomy vs. matched-pair 341 lobectomy) [16]; Choi et al. (5266 patients with papillary thyroid cancer tumors of 1–4 cm maximal diameter) [17]; Gartland et al. (systematic review of papillary thyroid cancer tumors of 1–4 cm in maximal diameter) [18]; and Vargas-Pinto et al. (systematic review of low-risk thyroid cancer) [19]. A recent publication by Zambeli-Ljepović et al. (2260 total thyroidectomy vs. 1081 lobectomy) demonstrated that routine use of total thyroidectomy for older adults with low-risk papillary thyroid cancer may lead to potentially avoidable complications and readmissions and suggested that in many cases, a lobectomy may be a safer, less costly alternative while still maintaining excellent prognostic outcomes [20].

Since papillary microcarcinomas are often multifocal and bilateral, it is not surprising that patients treated with thyroid lobectomy may have a slightly higher rate of structural disease detection during follow-up assessments, approximating for 1–4% of patients who were properly selected for lobectomy [14, 21, 22]. These local-regional recurrences or small, persistent disease foci are easily detected by neck ultrasonography and may be treated with appropriate surgery in the future if they become clinically relevant. These local-regional recurrences are not associated with a significant increase in disease-specific mortality.

Clinical Framework to Guide Decision-Making Processes Regarding the Extent of Initial Surgery for Differentiated Thyroid Cancer

We previously developed and validated a clinical framework to guide patient selection and risk stratification for active surveillance management of low-risk thyroid cancer [5, 6]. Patients who would be candidates for an observational management program would also likely be good candidates for minimalistic, surgical approaches, such as a hemithyroidectomy. Unlike patients selected for active surveillance, patients selected for hemithyroidectomy will have additional information available in both the intra-operative and postoperative periods that could impact the final decision on being classified as ideal, appropriate, or inappropriate for a thyroid lobectomy (Fig. 4.1). It is important for patients who undergo hemithyroidectomy to understand that the final determination whether hemithyroidectomy was the appropriate and sufficient initial operation is a multistep process that cannot be finalized until several weeks after surgery once the pathology report becomes available for review and discussion. Patients who are uncomfortable with this degree of uncertainty often have selected a total thyroidectomy as their initial surgical procedure. To minimize the need for an immediate completion thyroidectomy, we encourage patients to empower their surgeon to move from a hemithyroidectomy to a total thyroidectomy as the initial surgical procedure if there is intra-operative evidence of gross extrathyroidal extension or clinically significant lymph node metastases.

We found it very useful during our discussions with patients regarding minimalistic management options to evaluate their medical decision-making by using the constructs described in the book, *Your Medical Mind: How to Decide What Is Right for You* by Jerome Groopman and Pamela Hartzband [23, 24]. This book characterizes patients as [1] medical maximalists or medical minimalists, [2] believers or doubters, and [3] embracing technology or having a naturalistic orientation (see the online video lecture: https://videocast.nih.gov/watch=15339) [25]. Most patients who select more aggressive upfront therapies often express views identifying them as medical maximalists and endorse concepts such as being proactive about their health, believing that more is usually better, and desiring to be ahead of the curve in treating medical issues. They are further characterized as technology-oriented believers when it comes to being confident that surgery can be performed safely with few complications and that the postoperative course will be unremarkable. Most patients who choose a less aggressive management option, however, tend to endorse minimalistic concepts that favor the surveillance of their disease until it is clear that immediate therapy is mandatory, believe that less is more, and often are very interested in nontraditional therapies, such as herbs, natural products, exercise, yoga, and dietary modifications. Interestingly, for certain patients with differentiated thyroid cancer who identify as a minimalist, a transoral endoscopic thyroid surgery vestibular approach (TOETVA), a technique designed to eliminate an external scar, is deemed preferable to more traditional open thyroid surgery [26, 27].

We also believe it is important to recognize that each clinician has a unique intrinsic personal medical decision bias (including identifying as a maximalist or minimalist) that could subliminally impact their willingness to accept or endorse certain therapeutic management options. Interestingly, the options recommended to patients are often different than those they would recommend for themselves or their family members. From our perspective, it appears that patients process the information given them by their medical team about tumor characteristics, as well as the team's philosophy and recommendations, through this medical decision-making filter to arrive at a final decision for a treatment plan.

The disease management team's final recommendations regarding the need for RAI ablation or adjuvant therapy require the evaluation of histological features that cannot be assessed in the preoperative or intra-operative setting, such as minor extrathyroidal extension, vascular invasion, multifocality, microscopic lymph node metastases, or more aggressive histological subtypes of differentiated thyroid cancer. Thus, to obtain proper informed consent, patients need to understand that the philosophy of their disease management team's approach regarding the need for RAI therapy and highly sensitive follow-up studies will have an immediate and direct impact on the likelihood that a patient will need a completion thyroidectomy in the first few weeks after a lobectomy.

Step 1: Preoperative Evaluation

The first step in determining whether the patient is an appropriate candidate for a minimalistic, initial surgical intervention is to evaluate the same three major domains in the clinical framework that we have previously described to facilitate the selection of patients, which takes into account tumor and imaging results, patient characteristics and preferences, and disease management team characteristics (Table 4.1) [5, 6]. A careful evaluation of the factors underlying each of these important domains can allow the patient to be classified as either an ideal, appropriate, or inappropriate candidate for a hemithyroidectomy.

The ideal patient is a motivated medical minimalist with intrathyroidal papillary microcarcinoma and no evidence on imaging (usually only neck ultrasound) of other abnormalities either within the thyroid or in the surrounding cervical lymph nodes. An ideal patient is cared for by a disease management team with extensive experience in evaluating and treating thyroid cancer with a minimalistic treatment philosophy. Ideal patients are willing to accept that a completion thyroidectomy may be needed based on either intra-operative or postoperative findings and understand that the risk of needing an immediate completion thyroidectomy is low given the treatment philosophy of their disease management team. Furthermore, they have normal thyroid function tests prior to surgery with no evidence of antithyroid antibodies, making them less likely to require thyroid hormone therapy after surgery.

Patients who are inappropriate candidates for a lobectomy have preoperative or intra-operative evidence of extrathyroidal extension, clinically significant lymph

Table 4.1 Preoperative classification system for differentiated thyroid cancer: proper patient selection for a hemithyroidectomy (thyroid lobectomy ± isthmusectomy)

Patient classification	Tumor and imaging characteristics	Patient characteristics and preferences	Disease management team characteristics
Ideal	Classic papillary thyroid cancer <1 cm in maximal diameter Intrathyroidal No other abnormalities observed on neck US imaging Clinical N0 neck	Medical minimalist Motivated patient Willingness to accept possibility of a small volume of disease in the contralateral thyroid lobe Desire to preserve normal thyroid function Desire to avoid dependency on thyroid hormone replacement Desire to minimize surgical complications Open to intra-operative decision-making Willing to accept a low risk of needing an immediate completion thyroidectomy based on histological findings TSH level <2 mIU/L Undetectable antithyroid antibodies Undetectable anti-Tg antibodies	Experienced disease management team Experienced ultrasonography team Shared treatment philosophy (minimalist) Treatment team very selectively uses RAI for ablation or adjuvant therapy and follow-up management Availability of frozen section for intra-operative examination of cervical lymph nodes if needed
Appropriate	Papillary thyroid cancer subtypes 1–4 cm in maximal diameter Benign-appearing changes on US imaging (e.g., thyroiditis, benign-appearing thyroid nodules) Clinical N0 neck	Medical minimalist or maximalist Desire to keep normal thyroid function (or to avoid surgical complications) outweighs the concern for disease in the contralateral thyroid lobe or the desire for RAI TSH level >2 mIU/mL Presence of antithyroid antibodies Presence of anti-Tg antibodies	Clinicians agree on a minimalistic, postoperative management plan Unlikely to require RAI Comfortable that follow-up US is adequate for patients with low risk
Inappropriate	Extrathyroidal extension Clinical N1 metastases Distant metastases High-risk molecular profile	Medical maximalist Patient desires a total thyroidectomy and/or RAI Clinical indications for RAI for ablation/adjuvant therapy/staging	Treatment team anticipates the need to recommend RAI for ablation, adjuvant therapy, staging, or follow-up management

Abbreviations: N0, staging with no evidence of regional lymph node metastasis; N1, staging with evidence of metastasis to regional lymph nodes; RAI, radioactive iodine; Tg, thyroglobulin; TSH, thyroid-stimulating hormone; US, ultrasound

node metastasis, or distant metastasis. We anticipate specific molecular profiles will be identified in the future to help determine if a patient is an inappropriate candidate for a lobectomy, but there are currently no specific molecular profiles that have been identified to exclude an otherwise appropriate patient from having a thyroid lobectomy. Molecular profiling of tumors, therefore, is not mandated prior to deciding the extent of a thyroidectomy. Patients who are medical maximalists would generally be inappropriate for a hemithyroidectomy, as they likely will be more reassured with a total thyroidectomy and often will opt for RAI scanning, RAI ablation, or adjuvant therapy.

Identifying the ideal patients and the clearly inappropriate patients leaves a large group whom we classify as appropriate for a hemithyroidectomy (Table 4.1). These patients are neither ideal candidates for a hemithyroidectomy, nor do they demonstrate features that would make them inappropriate candidates for a hemithyroidectomy. We often frame our discussion with these patients as an evaluation of "two right answers" by reviewing the risks and benefits of each approach and integrating the patient's preferences, values, and medical decision-making construct (minimalist vs. maximalist) to arrive at the "best answer" for their surgical intervention. We reassure patients who are appropriate candidates for a hemithyroidectomy that the choice of either a lobectomy or a total thyroidectomy will result in the same, excellent oncologic outcomes, and this concept is reaffirmed to patients who undergo a lobectomy and have the option to undergo a completion thyroidectomy without major complications if necessary.

Step 2: Intra-operative Evaluation

Patients who are ideal or appropriate candidates for a hemithyroidectomy based on preoperative evaluation and patient preference are encouraged to empower their surgeon to proceed with an initial total thyroidectomy if their intra-operative findings reclassify them as inappropriate for a minimalistic management approach. While not common, an upfront total thyroidectomy with compartment-oriented neck dissection (if indicated) would be recommended if there is identification of unexpected gross extrathyroidal extension or clinically apparent metastatic lymph nodes (cN1) that were not identified preoperatively.

It is very important for patients and their family to have a clear plan for how to proceed if they are faced with these unexpected intra-operative findings. Most patients will consent for a hemithyroidectomy or a total thyroidectomy with or without an indicated compartment-oriented neck dissection to undergo the appropriate oncological surgery at the first setting and to minimize the need for a completion thyroidectomy. However, we occasionally encounter a well-informed patient that will consent only for a hemithyroidectomy regardless of the intra-operative findings

deferring the decision regarding completion thyroidectomy until they are able to participate in a subsequent discussion of the risk and benefits of additional surgery and/or radioactive iodine therapy based on their understanding of the intra-operative findings and the tumor histology.

Step 3: Postoperative Evaluation

The pathology report provides the primary source of key informational risk factors that determine whether a hemithyroidectomy was the best initial management option. Based on proper preoperative evaluations and intra-operative decision-making, patients with large tumors (>4 cm in maximal diameter), evidence of gross extrathyroidal extension, and clinically significant lymph node metastases will already have been identified and consequently undergone a total thyroidectomy. What remains are intrathyroidal tumors that are less than 4 cm in maximal dimension and are either with or without evidence of a very small volume of lymph node metastases and/or worrisome histological features that can only be seen on microscopic examination of the tumors.

A review of the histological features provides important information regarding risk stratification, such as risk of recurrence and risk of disease-specific mortality. From a practical standpoint, however, the primary driver of whether an immediate completion thyroidectomy should be recommended is based on the perceived need for RAI scanning, remnant ablation, or RAI therapy by the disease management team and/or the patient. A completion thyroidectomy also allows for more sensitive and specific evaluation of the postoperative thyroglobulin level, which can be important to determine the need for RAI scanning or therapy in some clinical scenarios.

Indications for RAI scanning or therapy usually mandate a completion thyroidectomy since they are ineffective in the setting of a residual thyroid lobe. While it is possible to destroy a normal thyroid lobe with RAI therapy, [28] we prefer a surgical completion thyroidectomy as the most expeditious approach to subsequent RAI therapy in most cases.

As detailed in Table 4.2, the disease management team at Memorial Sloan Kettering Cancer Center in New York developed a shared consensus regarding how to classify tumor-specific pathological features as ideal, appropriate, or inappropriate for a hemithyroidectomy. These histological features largely correlate with our perceived need of whether RAI scanning or therapy is likely to benefit a patient. For example, we do not recommend RAI scanning for patients with ideal histological features who would be classified as ideal candidates for a hemithyroidectomy. Conversely, a surgical completion thyroidectomy would be recommended for patients with inappropriate histological features, since RAI therapy is routinely used in this setting. Patients with appropriate histological features will have the choice of deciding whether a completion thyroidectomy may be beneficial to facilitate RAI scanning, RAI treatment, or follow-up. These features correspond to the

Table 4.2 Postoperative histological confirmation of proper patient selection following a hemithyroidectomy (thyroid lobectomy ± isthmusectomy) for differentiated thyroid cancer

Patient classification	Characteristic
Ideal	Intrathyroidal unifocal or multifocal papillary microcarcinoma with or without *BRAF* V600E mutation Intrathyroidal FV-PTC with capsular invasion only (no vascular invasion) NIFT-P Intrathyroidal, well-differentiated FTC (invasion of tumor capsule without vascular invasion) Clinical N0 and pathologic N0/Nx neck Small, differentiated thyroid cancers confined to the isthmus
Appropriate	Intrathyroidal PTC tumors at 1–4 cm in maximal diameter Minor extrathyroidal extension Clinical N0 but pathologic N1 micrometastases (includes pN1a and pN1b disease with ≤5 microscopic lymph node metastases, all of which are <0.5 cm in maximum diameter) FV-PTC, FTC, or PTC with minor vascular invasion (<4 microscopic foci of vascular invasion) Intrathyroidal tumors at 1–2 cm in maximal diameter, with potentially aggressive histological variants (e.g., tall cell variant, hobnail variant, columnar cell variant)
Inappropriate	Extensive vascular invasion (FTC or HCC with ≥4 microscopic foci of vascular invasion) Larger primary tumor >2 cm in maximal diameter, with potentially aggressive variants (e.g., poorly differentiated thyroid cancer, tall cell variant, hobnail variant, diffuse sclerosing variant, or columnar cell variant) Clinical N1 or pathologic N1 disease (includes N1a and N1b disease involving >5 lymph node metastases or any lymph node metastasis >0.5 cm in maximum diameter) Gross extrathyroidal extension

Abbreviations: *FTC* follicular thyroid carcinoma, *FV-PTC* follicular variant of papillary thyroid carcinoma, *HCC* hepatocellular carcinoma, *NIFT-P* noninvasive follicular thyroid neoplasm with papillary-like nuclear features, *N0* staging with no evidence of regional lymph node metastasis, *N1* staging with evidence of metastasis to regional lymph nodes, *N1a* staging with evidence of metastasis to level VI or VII lymph nodes, *N1b* staging with evidence of metastasis to unilateral, bilateral, or contralateral lateral neck lymph nodes or retropharyngeal lymph nodes, *Nx* staging of regional lymph nodes that cannot be assessed, *pN* pathologic staging of regional lymph nodes, *PTC* papillary thyroid carcinoma

ATA and NCCN guidelines for the selective use of RAI ablation or adjuvant therapy, which should be considered and potentially recommended based on the careful assessment of the risks and benefits of each case [2, 3].

Ideal histological features include small, intrathyroidal well-differentiated thyroid cancer tumors (<1 cm in maximal diameter) with no evidence of extrathyroidal extension, lymph node metastases, or worrisome histological subtypes. Since more than 50% of papillary microcarcinomas harbor *BRAF* V600E mutations and the vast majority display an indolent biological behavior, we consider classic papillary thyroid cancer with *BRAF* V600E mutations to be in the ideal category. Ideal patients are considered low risk in the modified 2009 ATA Risk Stratification System [2].

Neither the ATA nor NCCN guidelines require total thyroidectomy, RAI ablation, or adjuvant RAI therapy in patients with these ideal histological characteristics [2, 3].

Most patients with inappropriate histological features have been identified in the preoperative or intra-operative setting due to the presence of gross extrathyroidal extension or a clinically apparent cervical lymph node metastasis (cN1). It is unusual for potentially aggressive variant tumors that are greater than 2 cm in maximal diameter to be seen without some evidence of local invasion or lymph node metastases on preoperative or intra-operative evaluations. However, the unexpected presence of extensive vascular invasion in a well-defined, intrathyroidal tumor is the most common reason to recommend a completion thyroidectomy since the presence of microscopic vascular invasion cannot be assessed by preoperative or intra-operative evaluations. It is very unusual to observe extensive vascular invasion in tumors that are 1–2 cm in maximal diameter; therefore, this indication for a completion thyroidectomy is most commonly seen in larger tumors that are 2–4 cm in maximal diameter. More than 70% of patients with papillary microcarcinoma will have micrometastases identified that have little clinical significance, if meticulous prophylactic central neck dissections are performed [29]. The identification of these small lymph node metastases in patients who otherwise appeared to have no evidence of regional lymph node metastasis in the neck (staging of N0 neck) is expected, and they do not require treatment with a completion thyroidectomy or RAI ablation; these patients can be followed as low risk of recurrence cases.

None of the individual histological features that we have classified as appropriate for a hemithyroidectomy are considered as absolute indications for a completion thyroidectomy and RAI treatment. We do not routinely recommend RAI for most cases even if a total thyroidectomy had been done and the pathology report had identified these features. These features are individually associated with a slightly increased risk of recurrence; therefore, we acknowledge that some patients and some disease management teams would classify some (or all) of these features as indications for RAI. It is therefore important for each disease management team to determine in advance which histological features would be considered as appropriate or inappropriate for minimalistic initial management.

Patients with “appropriate histological characteristics” may therefore be offered an active surveillance approach or a completion thyroidectomy based on the treatment philosophy of the disease management team, the values and preferences of each patient, and the combination of worrisome histological features. Although it is not mandatory, a completion thyroidectomy is preferred by some patients and clinicians to facilitate the use of RAI even if both the size and number of lymph node metastases are small. As consistent with a selective management approach, the ATA guidelines also specify that “in addition to standard clinicopathologic features, local factors such as the quality of preoperative and postoperative ultrasound evaluations, availability and quality of thyroglobulin measurements, experience of the operating surgeon, and clinical concerns of the local disease management team may also be considerations in postoperative RAI decision-making” [2].

Prior studies that have used our postoperative histological classification system (Table 4.2) report immediate completion thyroidectomy rates that have been as low as 6% [14, 21]. However, when criteria that we consider to fall under the classification of appropriate for hemithyroidectomy are used to mandate completion thyroidectomy, the likelihood of needing an immediate completion thyroidectomy has varied between different groups, with rates as high as 20% [30, 31], 44% [32], or 60% [33].

Typically 6–12 weeks after a thyroid lobectomy, a non-stimulated serum thyroglobulin measurement is obtained even though it is neither a highly sensitive nor specific marker of persistent disease [7, 8]. The primary use of the postoperative serum thyroglobulin measurement is to identify the very few patients with otherwise ideal or appropriate tumor types who have distant metastases which can be identified by the presence of very elevated serum thyroglobulin levels in the absence of known benign thyroid nodules or malignant thyroid disease. In the absence of benign thyroid nodules in the remaining contralateral lobe, non-stimulated, postoperative serum thyroglobulin values are seldom more than 30 ng/mL and are more commonly less than 10 ng/mL. Serum thyroglobulin values in the hundreds or thousands should prompt re-evaluation to rule out the presence of distant metastases.

Follow-Up Recommendations Following Hemithyroidectomy

Even with careful preoperative, intra-operative, and immediate postoperative risk stratification, as many as 10–20% of patients selected for hemithyroidectomy will have persistent disease identified either in the contralateral lobe or in cervical lymph node metastases over 10–20 years of follow-up. These recurrences are usually easily detectable by either occasional neck ultrasonography (small volume of persistent disease) or a physical examination, at which point salvage therapy is very effective and can be employed with no impact on disease-specific survival. While the presence of distant recurrences in this group of patients is very uncommon, occurring probably in less than 1% of patients who are older than 30 years, they should be detected by serial measurements of serum thyroglobulin levels that show a consistent rise over time. It is therefore necessary to have judicious use of follow-up imaging (usually neck ultrasonography) and biochemical markers (thyroglobulin and thyroglobulin antibody evaluations) during the years following a lobectomy as outlined in Table 4.3.

We do not require patients who have undergone hemithyroidectomy and have no evidence of structurally identifiable disease to undergo thyroid-stimulating hormone (TSH)-suppressive therapy [34]. Levothyroxine therapy is initiated to avoid excess TSH stimulation only if the baseline postoperative TSH value is consistently above 3 mIU/mL [35, 36]. If the 6-week TSH value is in the 3–5 mIU/mL range, a repeat TSH evaluation is performed 2–3 months later and often shows that mild compensation of the contralateral lobe has resulted in a TSH value of less than 3 mIU/mL.

Table 4.3 A practical approach to follow-up management after a thyroid lobectomy

Follow-up management	Details
TSH goal	0.5–3.0 mIU/mL With or without levothyroxine
Clinic visits	6–12 weeks (to review pathology and check TSH and Tg levels) Then 6–12-month follow-up evaluations Yearly follow-up evaluation with a physical examination for 2–3 years Evaluate TSH, free T4, Tg, and TgAb levels at each clinic visit
Imaging	Neck US at 6–12 months, 3 years, and 5 years Then very rarely
Indications for a future completion thyroidectomy	Physical examination findings Neck US findings Sustained, serial rise in Tg levels over time

Abbreviations: *T4* thyroxine, *Tg* thyroglobulin, *TgAb* thyroglobulin antibody, *TSH* thyroid-stimulating hormone, *US* ultrasound

Indications for a future completion thyroidectomy usually are identified by the result of physical examination or ultrasonographic evidence of persistent thyroid cancer. Although a sustained serial rise in thyroglobulin levels over time is an indication for a completion thyroidectomy, this is a nonspecific finding that is most often related to benign thyroid nodules in the contralateral lobe instead of metastatic disease [37]. Since this cannot be known a priori, a completion thyroidectomy with re-evaluation of both thyroglobulin levels and the pathology report following surgery is usually recommended if persistent increases in thyroglobulin are documented over time.

Conclusions

Clinical frameworks can serve as useful tools to foster discussion, understanding, and use of risk stratification as we strive to match the aggressiveness of our treatment interventions with the expected biological behavior of each individual patient's thyroid cancer. A thoughtful evaluation of tumor and imaging results, patient characteristics and preferences, and disease management team characteristics and treatment philosophy will guide the proper identification of patients who are most likely to benefit from less aggressive treatment options, such as a hemithyroidectomy for well-differentiated thyroid cancer. The integration of careful preoperative, intraoperative, and postoperative evaluations will allow patients to be classified as ideal, appropriate, or inappropriate for minimalistic treatment options. To minimize the need for an immediate completion thyroidectomy, it is critical for patients and their disease management team to understand the intra-operative and postoperative factors that would mandate a completion thyroidectomy. This approach will lead to

optimized and personalized patient management, in which the risks and benefits of the treatment options are balanced against the expected patient-specific biological behavior of thyroid cancer.

Financial Disclosure The authors have no relevant financial conflicts of interest to disclose.

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Chapter 5
Neoadjuvant Therapy for Anaplastic Thyroid Carcinoma

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Introduction

Anaplastic thyroid cancer (ATC) accounts for approximately 1–2% of all thyroid cancers in the United States, while the prevalence ranges from 1% to 10% worldwide [1]. Though rare, ATC remains a deadly disease, accounting for over half of annual deaths from thyroid carcinoma.

ATC has been demonstrated to arise in patients with a history of thyroid pathology. Some have shown that up to 80% of ATC occurs in the presence of a known concurrent well-differentiated thyroid carcinoma (WDTC) or in patients who have been treated for WDTC or poorly differentiated thyroid carcinoma [2, 3]. It has thus been hypothesized that ATC may develop from dedifferentiation of existing WDTC. Meticulous study of these molecular pathways has yielded a group of biologic targets, some of which have led to the development of several promising pharmacologic interventions.

ATC portends a grave prognosis with historical median survival of 5 months and 20% 1-year survival [1]. Despite this, it has been shown that the extent of surgical resection and feasibility of complete resection are significant positive predictors of prolonged survival [4–7]. Unfortunately, over 80% of patients with ATC present with locally invasive disease making surgical resection difficult or impossible [6, 7]. In this context, external beam radiation has been the standard of care. However, upfront neoadjuvant therapy has become a promising tool in management. While surgery and radiation remain a mainstay of treatment [8], advances in the

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M. C. Singer, D. J. Terris (eds.), *Innovations in Modern Endocrine Surgery*,
https://doi.org/10.1007/978-3-030-73951-5_5

understanding of the molecular pathogenesis of ATC have added to the arsenal available to clinicians to help patients with previously unresectable disease. In this chapter, these treatments and their clinical utility within the realm of neoadjuvant therapy will be explored.

Clinical Presentation, Histopathology, and Staging of Advanced ATC

A majority of patients with ATC present with locally invasive disease [6]. A history of a rapidly enlarging neck mass is common (Figure 5.1a–c). Some degree of dysphagia, odynophagia, and dysphonia is usually evident and is sometimes accompanied by stridor. Distant metastasis is evident in at least 40% or more of patients at presentation[9]. Positive prognostic factors include age <60 years, intrathyroidal tumors <5 cm, complete surgical resection, and use of multimodal therapy [9–11].

Although the histopathology of ATC is beyond the scope of this chapter, it is important to understand that confirmation is necessary not only to aid in prognostication for the patient but also to appropriately direct treatment. Several diseases can mimic ATC, including squamous cell carcinoma of the thyroid, lymphoma, neuroendocrine tumors, or metastatic carcinoma [12]. Histopathology will likely reveal one of three growth patterns, including spindle cell, pleomorphic, and squamoid patterns [13]. Adjacent foci of WDTC may be identified, confirming the diagnosis of ATC. Immunohistochemistry often further aids in the identification of ATC.

ATC remains a lethal disease, and the American Joint Committee on Cancer (AJCC) staging reflects this. All ATCs are classified as stage IV disease: IVA tumors

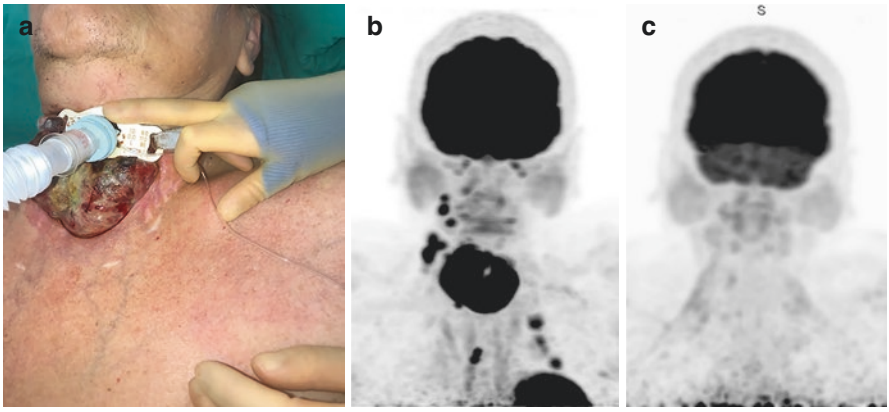

Fig. 5.1 A 53-year-old patient with ATC presented with tumor invading the larynx and skin and airway obstruction requiring a tracheostomy (**a**). A Positron Emission Tomography (PET) scan demonstrated extensive and invasive neck disease, as well as pulmonary metastases (**b**). Six months after Dabrafenib + Trametinib (DT), the patient with no evidence of metabolic neck or pulmonary disease (**c**)

are intrathyroidal, IVB tumors have gross extrathyroidal extension, and patients with IVC tumors have distant metastasis [12]. The extent and degree of surgical resection in patients undergoing primary surgery have also been clearly identified as a significant predictor of survival status for many different types of cancer (including ATC), and thus, the AJCC has developed a separate classification system of extent of surgical resection. R0 indicates absence of residual tumor, whereas R1 indicates microscopic persistent disease and R2 macroscopic residual disease [12].

Molecular Pathogenesis

A multitude of clinical, molecular, and epidemiologic studies have shown that a large majority of ATC represents a progressive stepwise dedifferentiation from WDTC into poorly differentiated carcinoma [14–17]. Indeed, next-generation sequencing has confirmed that ATC develops due to an accumulation of several key somatic mutations, some of which have therapeutic significance as we will see later [18]. We have presented here a summary of genetic markers, which is not an exhaustive list, but hopefully serves to create a foundation for understanding the complexity of ATC as well as the basis of novel neoadjuvant therapy.

The link between papillary thyroid carcinoma (PTC) and ATC has been confirmed by a myriad of previous studies [19, 20]. Of the known genetic alterations common to both PTC and ATC, $BRAF^{V600E}$ mutation is perhaps one of the most notorious and has been found to occur in approximately 60% of PTC [21, 22] and approximately 40% of ATC. $BRAF^{V600E}$ is a tyrosine kinase and is a known oncogene which is present in several other malignancies, including melanoma [23]. In patients with concurrent WDTC and ATC, $BRAF^{V600E}$ mutations have been found in both components of same tumor, suggesting that $BRAF^{V600E}$ plays a key role in the pathogenesis of ATC development [21].

The *RAS* (N, H, and K) genes have also garnered significant attention. *RAS* mutations have been found in up to 30% of ATC and were detected first in follicular carcinoma and follicular PTC variants [24, 25]. *RAS* mutations function upstream of the *MAP-K* and *PI3K/mTOR* pathway causing continuous stimulation of this cascade resulting in tumorigenesis [21]. Not surprisingly, *mTOR* pathway aberrations have been found to be associated with tumorigenesis in several human malignancies including melanoma, breast cancer, and prostate cancer [21, 26–28]. Interestingly, a recent whole-exome sequencing study of 22 patients with ATC revealed two dichotomous genomic groups: all exhibited either *RAS* and *TP53* mutations or $BRAF^{V600E}$ and *TP53* mutations [29]. Further, Wang and colleagues showed a 56% preponderance of *TP53* mutations in ATC [24]. The role of *TP53* as a tumor suppressor has been well described in almost every known human malignancy and is the most common gene mutation across all cancer types [30, 31].

Several other genes have been associated with WDTC and progression to ATC. Among these, *RET-PTC*, *NTRK*, *PAX8-PPARγ*, *ALK fusions*, *and TERT* promoter mutations have been studied extensively [14, 16, 17, 29, 32–35]. Combinations

of these mutations have been shown previously to have a synergistic effect, often resulting in a more aggressive phenotype [36]. In addition, numerous sporadic mutations and epigenetic changes are described extensively in the literature and remain an area of active interest [15].

Neoadjuvant Therapy

In patients with advanced disease at presentation, previous treatment paradigms for ATC dictated either morbid up-front surgery, palliative chemoXRT, or hospice care. Yet, with the advent of improved molecular understanding of ATC and novel therapeutics, several promising treatment options are available in patients with locally advanced ATC. Thus, most patients should not be offered hospice up front. For purposes of this discussion, neoadjuvant therapy will be considered treatment rendered prior to definitive surgery.

External Beam Radiation

Management of ATC has classically involved trimodal therapy, including some combination of surgery, chemotherapy, and radiation [5, 6, 37, 38]. In the preoperative setting, the efficacy of several traditional protocols has been studied for over 20 years. Tennvall and colleagues looked at the efficacy of three protocols in 55 patients, two in which preoperative radiotherapy was administered to total dose of 30 Gy with weekly doxorubicin followed by surgery and postoperative radiation to a total of 46 Gy and the third in which the entire dose of radiation was given preoperatively with weekly doxorubicin followed by surgery [38]. They found a significant difference in rates of local control: 52% of the former protocol had recurred within 2 years, whereas only 23% of patients had recurred in that same period in the latter protocol. This suggested that a hyperfractionated and accelerated radiation course in the preoperative setting may improve local control in ATC. These findings were corroborated in a similar protocol by Kim and colleagues [39].

Cytotoxic Chemotherapy

Several systemic agents have also been studied in the neoadjuvant setting. In a study of 76 patients with ATC, Higashiyama and colleagues showed that weekly induction of paclitaxel followed by curative surgery and adjuvant radiation resulted in complete response in 44% of patients with IVB disease [40]. When compared to patients who had not received induction therapy or those who had received a different chemotherapeutic agent, there was a significant overall survival advantage in the

induction of paclitaxel group. All IVC patients were dead of disease within 8 months regardless of induction agent used.

BRAF-Directed Therapy

The selective BRAF^{V600E}/MEK inhibitor combination was approved by the FDA in 2018 for BRAF^{V600E}-mutated ATC, based on the results of a small phase 2 basket trial. In this trial, of 16 patients with *BRAF*^{V600E}-mutated ATC treated with dabrafenib and trametinib (all patients had received prior radiation and/or surgery, and six had received prior systemic therapy), 69% of patients responded (one complete responder), with 80% overall survival at 1 year [41]. The most commonly observed adverse effects were fatigue, pyrexia, and nausea in less than 40% of patients. The neoadjuvant use of these drugs was first described in a case report [42]. In a patient with initially end-stage, unresectable (carotid encasement, supraglottic and pyriform direct extension) ATC, the use of dabrafenib and trametinib induced an initial impressive partial response; however, the patient developed resistance soon after, at which point, the checkpoint inhibitor, pembrolizumab (anti-PD1), was added to the regimen. The patient responded again and then underwent complete surgical resection with negative (R0) margins [42]. The addition of pembrolizumab has been shown to be potentially efficacious in a subset of ATC patients. In a retrospective study of 12 ATC patients with progression on their kinase inhibitor therapy, the addition of pembrolizumab yielded a partial response in 5 of 12 patients (42%), stable disease in 4 of 12 (33%), and progression in 3 of 12 (25%) with a median overall survival of 10.4 months [43]. This suggests that the mechanism of kinase inhibitor resistance may be mediated by cell checkpoint dysregulation and that the addition of checkpoint inhibitors in these patients may result in significant differential response, particularly in terms of the length of time before development of resistance.

A larger series with six patients was later reported with promising results [44]. In this series, six consecutive patients with *BRAF*^{V600E}-mutated ATC received dabrafenib and trametinib followed by complete surgical resection (R0) in all patients. Three also received pembrolizumab. Overall survival at 6 months was 100% and 83% at 1 year; two patients died of distant metastasis without evidence of locoregional disease at 8 and 14 months from diagnosis. All other patients remained free of disease at last follow-up.

The landscape of multidisciplinary management of ATC has been revolutionized over the last 5 years, as documented by a recent single institution study of 479 patients over the last 20 years, representing the largest single institution study of ATC to date[45]. In this retrospective cohort study, overall survival at 1 and 2 years was significantly different among treatment eras: 35% and 18% in the 2000–2013 group, 47% and 25% in the 2014–2016 group, and 59% and 42% in the 2017–2019 group, respectively. Factors associated with improved OS included targeted therapy, the addition of immunotherapy to targeted therapy, and surgery following

neoadjuvant *BRAF*^{V600E}-directed therapy. Median follow-up of patients undergoing surgery following neoadjuvant *BRAF*^{V600E}-directed therapy was 1.21 years with a 94% 1-year survival [45].

In patients with stage IVA disease, the authors suggest surgery up front with adjuvant radiation (+/−chemo)therapy. In patients with stage IVB or IVC and *BRAF*^{V600E}mutations, the authors suggest neoadjuvant BRAFi/MEKi +/− immunotherapy, followed by evaluation of tumor resectability. At least two-thirds of patients with initially unresectable disease (carotid encasement, mediastinal vessel involvement, prevertebral fascia involvement) or laryngotracheal involvement will become resectable (R0 or R1 resection) following neoadjuvant BRAFi/MEKi +/− immunotherapy. These cases will very rarely require a more complex surgery and recovery such as with a laryngectomy or tracheal resection. Patients on BRAFi/MEKi +/− immunotherapy undergo surgery after reaching an apex in radiographic response, typically about 3–5 months following initiation of therapy. Resistance to therapy with disease progression (after initial significant response) can begin as early as 3 months, so patients should be monitored closely during this time, and surgery should be recommended before disease progression. Patients with distant metastasis (stage IVC) who have had complete or near-complete radiographic response at distant sites are still offered surgery to consolidate locoregional control, with resumption of BRAFi/MEKi +/− immunotherapy as soon as possible after surgery (generally at 1 week postoperatively after drain removal). Postoperative adjuvant radiation therapy is considered on a case-by-case basis for BRAF^{V600E}-mutated stage IVB patients, while postoperative radiation therapy is almost never recommended for patients who had originally presented with stage IVC (distant metastatic) disease, regardless of whether they have had a complete metabolic response at distant sites. Finally, for BRAF^{V600E}-mutated tumors which remain unresectable (meaningful R0 or R1 resection not possible) following BRAFi/MEKi +/− immunotherapy (less than 25% of BRAF^{V600E}-mutated tumors), tumors with partial response should remain on BRAFi/MEKi therapy indefinitely, whereas those without response should be considered for alternative management.

Conclusion

The extremely aggressive natural history of ATC dictates not only a multidisciplinary approach to therapeutic management but also timely and effective intervention. For *BRAF*^{V600E}-mutated patients, the induction of rapid and dramatic response with BRAF^{V600E}/MEK inhibitors has opened the door for locoregional therapy and the possibility of long-term local disease control. However, cautious optimism must be used in this setting as drug resistance has been shown to be a potential pitfall and toxicity may limit treatment, though several phase II trials have shown favorable toxicity profiles. Recent tertiary care center multidisciplinary experience has demonstrated marked improvement in survival in ATC, owing to uniform and rapid molecular genetic testing, personalized targeted therapy for genetic mutations,

addition of immunotherapy, and the integration of surgery following neoadjuvant therapy. Further prospective, randomized clinical trials and scientific discovery are necessary to perpetuate the dramatic survival improvements witnessed over the last 5 years.

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Chapter 6
Nonoperative Thyroid Ablation Techniques for Benign Thyroid Nodules

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Introduction

Thyroid nodules occur commonly and are clinically palpable in about 5% of the population. However, the incidence of thyroid nodules is up to 60% when the thyroid gland is evaluated by high-resolution ultrasonography (US) [1, 2]. Fortunately, the majority of these nodules are small and benign (>95%) and do not need any additional treatment [1, 2]. Fine-needle aspiration (FNA) biopsy, if indicated based on size and the presence of suspicious sonographic features, can often confirm the benignity of most nodules [1–5].

However, there is a select group of patients with nodules that may grow and cause local pressure symptoms like neck pain, choking sensation, dyspnea, or dysphagia. A recent multicenter, observational study reported that up to 15% of benign nodules grow continuously, in an accelerated matter, while the rest remain relatively static in size [3].

Surgical resection has traditionally been the recommended treatment for symptomatic benign thyroid nodules. The American Thyroid Association (ATA) thyroid nodule guidelines recommend that surgical resection (in the form of a hemithyroidectomy or a total thyroidectomy) be considered when a benign solid or predominantly solid nodule either has become large in size (>4 cm in diameter) or is causing

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M. C. Singer, D. J. Terris (eds.), *Innovations in Modern Endocrine Surgery*,
https://doi.org/10.1007/978-3-030-73951-5_6

compressive local symptoms or clinical concern [2]. Although surgery is a relatively safe procedure, there are small potential risks like hypothyroidism, bleeding, infection, voice hoarseness from recurrent or superior laryngeal nerve injury, and hypoparathyroidism that may occur after surgery [6]. In addition, surgery exposes patients to the risk of general anesthesia and may not be feasible in some individuals because of underlying medical comorbidities [1–6].

To potentially obviate these risks, the development of less invasive, nonsurgical ablation techniques has been sought [7]. This has led to the introduction of procedures like percutaneous ethanol injection (PEIT) and image-guided thermal ablation techniques like laser ablation therapy (LAT), radiofrequency ablation (RFA), and high-intensity focused ultrasound (HIFU) ablation [7–11]. PEIT is effective and is recommended for recurrent, benign thyroid cysts [7, 8]. However, for solid or predominantly solid nodules, thermal ablation techniques like LAT and RFA are generally more effective [9–11]. The major benefits of these techniques over surgery are the preservation of normal thyroid parenchyma and function and the avoidance of a scar or wound [12].

Studies have shown that these nonsurgical approaches not only physically shrink the volume of the target tissue but also can alleviate pressure symptoms [9–11]. RFA has a well-established record of accomplishment of ablation of benign thyroid nodules [9]. It is undoubtedly the most popular form of ablation for this endeavor. On the other hand, HIFU is a relatively new technique for ablation. Its major advantage over other techniques is that it can induce a focused thermal tissue destruction of up to 85°C to treat a wide variety of benign and malignant tumors [14] while completely avoiding the placement of devices through the skin [13].

In this chapter, the selection criteria and details of HIFU and RFA are reviewed, and their safety and efficacy profiles in the treatment of benign thyroid nodules are discussed.

HIFU Ablation

Unlike other ablation techniques, HIFU utilizes focused US energy to generate heat [15]. This energy needs to traverse through the skin into the target nodule. The major advantage of this approach is that it does not need a needle or other instrument to be inserted into the target tissue. However, avoiding this instrumentation means that, at times, the energy delivery to the tissue can be less predictable than other forms of ablation. Currently, there is only one commercially available HIFU device, which is US guided (Fig. 6.1). The machine itself is a computer-driven system composed of an electronics cabinet, an extracorporeal probe (3 MHz frequency) mounted on a gantry and moved by stepper motors, a cooling unit, and an ultrasound imaging scanner (7.5 MHz 128-element imaging linear array).

Fig. 6.1 A treatment image captured immediately after an 8-second treatment pulse. The central panel represents the bird's-eye view reconstruction of the nodule. The empty circles represent the unablated subunits, while the filled circles represent the ablated subunits. Please also note the presence of hyperechoic marks (microbubbles) at the focal point of the HIFU beams in the treatment screen

Nodule Selection

The reported inclusion and exclusion criteria for the use of HIFU vary to a degree in the literature (Table 6.1) [16–21]. However, there are some consistent criteria that can be widely applied. In general, first, the target nodule has to be benign in nature. This typically is defined by a Bethesda class II result on FNA biopsy [15] within 3–6 months of treatment and a low or very low suspicion sonographic pattern on US [2]. Second, the thyroid enlargement (which can be either a solitary nodule or a dominant nodule in a multinodular gland) has to be causing compressive symptoms. Nonspecific neck complaints and/or cosmetic concerns alone are often not considered treatment indications for HIFU. Third, the index nodule has to have all three orthogonal dimensions ≥20 mm but ≤50 mm on US. For larger nodules, two sequential treatments would likely be necessary to manage the entire nodule [22]. Fourth, the solid component of the target nodule has to comprise ≥70% of its total volume on US. Nodules containing a larger fluid component are likely better managed by simple aspiration and ethanol injection. Fifth, the target nodule has to be

Table 6.1 A literature summary of HIFU studies adapting different criteria

First author (year)	Inclusion criteria	Exclusion criteria
Esnault (2011) [16]	At least two thyroid nodules, with at least one for surgery Nodule targeted for HIFU located at least 3 mm from the trachea, esophagus, recurrent nerve, carotid artery, and skin Selected nodule for HIFU treatment was different from the one indicated for surgery	Suspicion of malignancy nodule, neck irradiation, previous surgery, previous radioactive iodine treatment Any cystic components ≥20% or any large calcifications Patient unable to maintain a stable position with hyperextended neck
Korkusuz (2014) [17]	At least one benign thyroid nodule with associated thyrotoxicosis, neck pain, throat hoarseness, swallowing disorders, discomfort, and/or cost concern	Malignant nodule Close to heat-sensitive structures like the recurrent laryngeal nerve, trachea, esophagus, and carotid artery
Korkusuz (2015) [18]	Over 18 years old At least one benign thyroid nodule with associated issues neck pain, hoarseness, swallowing disorders, discomfort, cosmetic concerns, and/or thyrotoxicosis Refused surgery/RadioIodine Therapy (RIT)	Malignant nodules Target nodules close to sensible structures such as trachea and carotid arteries Patients who showed any contraindication to HIFU (recurrent nerve anomalies, target volumes not)
Korkusuz (2015) [19]	Patient with symptomatic nodule Cosmetic concerns Refused surgery or contraindicated	Patients with asymptomatic nodules Nodule volume ≥10 mL Histological evidence for malignancy
Kovatcheva (2015) [20]	Over 18 years old Presence of one or more thyroid nodules without signs of malignancy A nodule measured on US ≥10 mm in three orthogonal dimensions ≤30% of the targeted nodule is cystic HIFU accessibility of the targeted nodule Normal thyrotropin concentrations Absence of vocal cord immobility at laryngoscopy	Head and/or neck disease which prevents hyperextension of the neck Past medical history of thyroid cancer or other malignant tumors in the neck region History of neck irradiation Intranodular macrocalcifications which preclude treatment with HIFU Nodules next to posterior margin of the thyroid lobe with anteroposterior diameter less than 15 mm Pregnancy/lactation Any contraindications related to intravenous moderate sedation
Lang (2017) [21]	Benign cytology and low to very low suspicion sonographic pattern Nodule believed to be causing pressure symptoms All three dimensions between 10 and 40 mm Nodule ≥70% solidity Nodule within 5–30 mm from the skin Normal thyroid function and calcitonin levels	Age ≤18 years old Pregnant or lactating women Indeterminate or malignant nodules Intranodular macrocalcifications History of head and neck irradiation History of non-medullary thyroid carcinoma Preexisting vocal cord palsy

within the treatable depth for ablation (i.e., 5–30 mm between the skin and the nodule center). This is a requirement because HIFU is generally less effective with increased depth.

There is general consensus that pregnancy or lactation, indeterminate/malignant FNA results or intranodular macrocalcifications, a history of head and neck irradiation, a family history of non-medullary thyroid carcinoma, a preexisting vocal cord palsy, or any medical conditions which are contraindications for intravenous sedation all preclude treatment with HIFU.

Before Ablation

Before treatment, all thyroid enlargement is graded clinically. For clinical assessment, the World Health Organization (WHO) grading system is often used [23]. The important other aspect of clinical assessment is to measure the degree of pressure symptoms, using a visual analogue scale (VAS). Three orthogonal diameters of the target nodule (its longest diameter and two other perpendicular diameters) are then measured by US. In general, the longest diameter is the cranio-caudal dimension (length) of the nodule, while the other two perpendicular diameters are the mediolateral (width) and anteroposterior (depth) dimensions. To estimate nodule volume, we use the following formula: volume (mL) = (width (in cm) × depth (in cm) × length (in cm)) × (π/6) where π was taken as 3.1416. Apart from dimensions, the side and location of the nodule within the lobe (i.e., upper, middle, and lower thirds) and the number of other nodules >1 cm are recorded.

Evidence Supporting the Role of HIFU

Prior to clinical studies in humans, several animal studies were published to evaluate the feasibility of HIFU. Two animal studies demonstrated the ability of this technology to induce a well-defined lesion in a thyroid lobe without causing damage to the surrounding tissue [13, 15].

Clinical Application

Following these animal studies, an initial, small clinical study on 25 patients, scheduled to undergo thyroidectomy for benign multinodular goiter, was conducted [16]. All patients were subjected to HIFU treatment 2 weeks before their scheduled surgery. The amount of acoustic energy per pulse given to each nodule ranged from 35 to 94 joules. Thyroid US and thyroid function were evaluated before and after treatment. After surgery, macroscopic and histological examinations revealed that all

treated lesions were confined to the targeted area without affecting neighboring structures. Pathological analysis found that the extent of nodule destruction ranged from 2% to 80%. No major complications occurred, even when the highest energy level was employed [16].

Despite the success of this first human study, the general adoption of HIFU in routine clinical practice had been slow. In the United States, the US-guided HIFU device has yet to be approved by the Food and Drug Administration (FDA) as a treatment for benign thyroid nodules.

Efficacy of HIFU Ablation

For ablation, the generally accepted endpoints for measuring efficacy are the extent of nodule shrinkage (%) in the first year by serial US assessments and changes in pressure symptoms by VAS. Table 6.2 summarizes the treatment results reported in the literature.

A number of studies have demonstrated the ability of HIFU to significantly reduce thyroid nodule size [17, 19, 20]. This reduction has been shown to correlate with a concurrent improvement in compressive symptoms in at least one study [21]. Importantly, it appears that this reduction can be achieved while maintaining normal thyroid function in most patients [18]. Importantly, this procedure appears to be well tolerated by most patients in terms of post-procedure pain [18].

However, a number of important questions remain regarding the efficacy and sustainability of HIFU treatment. One concern is the relatively inconsistent results between patients. Studies have reported varying degrees of reduction in nodule size, from between approximately 10% and nearly 80% [17, 19–21]. Given that smaller-sized nodules tend to shrink proportionately more than larger-sized nodules after a single ablation treatment [24], it has been suggested that perhaps, applying two sequential treatments for larger-sized nodules may improve outcomes [20, 21]. Lang et al. reported the short-term results of two sequential treatments in nodules and found that, relative to a single ablation, the 6-month shrinkage rate was significantly greater (56.74% ± 11.47% vs. 43.49% ± 12.03%, $p = 0.004$). Treatment morbidity did not appear to increase as a result of the extra session [22]. With improved technique, treating two nodules simultaneously in a multinodular goiter also appears to be safe [25].

A second issue regarding HIFU is the sustainability of its impact over time. The medium- to long-term results following a single HIFU treatment are not well established. In contrast to other ablation techniques such as RFA or LA, it is unclear whether the initial shrinkage from HIFU ablation persists beyond 12 months. Given that nodule regrowth can occur after thermal ablation, it is important to evaluate the longer-term outcomes with HIFU. To date, only a single study has reported the medium-term efficacy after single HIFU ablations [26]. In that study, a total of 108 patients were analyzed and followed for 2 years. At 2 years, less than two-thirds (58.3%) of nodules had a smaller volume (by >4.5%) than at 12 months, while about

Table 6.2 A comparison of treatment, complications, and efficacy between different HIFU studies

First author (year)	No. of nodules	Nodule volume (mL)	Type of device and probe	Total amount of DIAE to each nodule (KJ)	Treatment time (minutes)	Complications	Efficacy (% reduction from baseline)
Esnault (2011) [16]	22	0.5–2.6	US-guided HIFU/3 MHz extracorporeal probe	35–94 J/pulse[a]		Pain, skin burn, cough, blisters	Feasibility study. Ablated nodules were examined on histology after 2 weeks
Korkusuz (2014) [17]	10	Median: 3.19 (range: 0.8–7.67)	US-guided HIFU/3 MHz extracorporeal probe	Median: 8.4 (range: 5.65–12.46)	Not reported	Pain	Not reported
Korkusuz (2015) [18]	9	Median: 3.5 (range: 0.8–7.7)	US-guided HIFU/3 MHz extracorporeal probe	Median: 9.9 (range: 5.7–12.5)	Median: 62 (range: 42–96)	Pain during treatment, reddening of the skin	Median: 48.8 (range: 11.4–75.0) at 3 months
Korkusuz (2015) [19]	12	Median: 3.4 (range: 0.6–5.0)	US-guided HIFU/3 MHz extracorporeal probe	–	–	None reported	Median: 55 at 3 months
Kovatcheva (2015) [20]	20	Mean: 4.96 ± 2.79 (range: 1.56–9.35)	US-guided HIFU/3 MHz extracorporeal probe	Mean: 16.4 ± 7.7 (range: 5.5–31.7)	Mean: 86.8 ± 31.7 (range: 37–152)	Subcutaneous edema, skin redness	Mean: 48.7 ± 24.3 at 6 months (after single ablation)
Lang (2017) [21]	22	Mean: 6.98 ± 4.04 (range: 1.68–16.76)	US-guided HIFU/3 MHz extracorporeal probe	Mean: 15.17 ± 6.90 (range 5.88–28.35)	Mean: 75.71 ± 34.20 (range: 48.751–53.25)	Pain, skin redness, minor neck swelling	Mean: 68.87 ± 15.27 at 12 months (following single ablation)

Abbreviations: *US-guided HIFU* ultrasound-guided high-intensity focused ultrasound, *DIAE* depth-independent acoustic energy

[a]Only power was provided. Total energy was not available

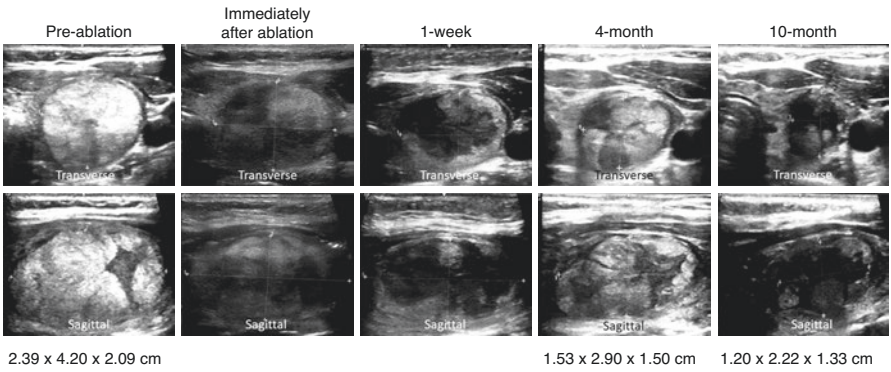

Fig. 6.2 Transverse ultrasound images of a left solid thyroid nodule obtained before treatment, 1 week, 4 months, and 10 months after HIFU treatment from a 37-year-old lady. Note the extent of nodule shrinkage and the echogenic change (from isoechoic to hypoechoic) after treatment

one-fifth of nodules (20.4%) demonstrated a small increase in volume compared to the volumes at 12 months [26]. However, the overall nodule reduction rates at 3, 6, 12, 18, and 24 months were 51.32% ± 20.71%, 62.99% ± 22.05%, 68.66% ± 18.48%, 69.76% ± 17.88%, and 70.41% ± 17.39%, respectively (Fig. 6.2).

Safety of HIFU Ablation

As with any intervention, the rate of complications of HIFU is critical to consider. Vocal cord paresis (VCP) is the most likely complication following HIFU ablation of thyroid nodules. The incidence of VCP after HIFU has been reported to be approximately 1–2% when the vocal cords are examined routinely after each procedure. This risk exists because the recurrent laryngeal nerve runs closely behind the thyroid lobe in the tracheoesophageal groove. If the targeted nodule is located near the posterior thyroid capsule, close to the tracheoesophageal groove, either induced heat or the HIFU wave itself can easily damage the nerve, resulting in VCP [27]. To minimize the risk of VCP, a safe distance of 1.1 cm between the focus of the beam and the tracheoesophageal groove should be maintained [27].

Other complications related to HIFU treatment, such as inadvertent skin burns and hypothyroidism, are rare. To avoid burning the skin, particular attention must be paid during treatment to possible changes of the target location caused by the patient's movement. Overshooting or undershooting of the nodule by the HIFU beam can cause inadvertent heat damage to the skin or deeper neck structures. A rise in the temperature of the skin surface may occur, and regular monitoring of skin changes is therefore crucial to prevent thermal injury. Fortunately, skin burns after HIFU ablation are extremely rare (<1%) when precautions have been taken.

Hypothyroidism as a direct result of HIFU ablation is very uncommon. This is because the HIFU beam is normally focused at the center of the target, without damaging the surrounding functional parenchyma. As a result, overall thyroid function remains unaltered after treatment in most patients [28].

Radiofrequency Ablation (RFA)

In contrast to HIFU, RFA is a more established ablation technique in the treatment of benign thyroid nodules. It relies on radiofrequency waves (usually 375–500 kHz) emitted from a needle electrode inserted into the target tissue [29]. In only a few seconds, RFA induces irreversible cell damage, with the local heat (60–100°C) generated from the agitation of tissue ions [6]. RFA devices and their electrodes are designed in such a way that higher temperatures (>100–110°C) are avoided. This is crucial because at higher temperatures, tissue vaporization and carbonization may actually impede the extent of ablation while at the same time increasing the chances of inadvertently damaging surrounding tissues [30–32].

RFA has been applied in many disease conditions like hepatocellular carcinoma and metastatic liver cancer. However, because the liver is a large organ, heat damage to adjacent vital structures is rare. Due to limited size of the thyroid gland, thinner, shorter and smaller, internally cooled electrodes need to be employed in order to avoid injury to critical surrounding structures [33].

In 2006, the first clinical use of RFA to manage benign, euthyroid nodules was described [34]. Like other ablation techniques, the main goals of thyroid RFA are to achieve nodule volume reduction and relief of compressive symptoms while avoiding surgery and its associated sequelae.

Nodule Selection

For RFA, like HIFU, only cytologically benign thyroid nodules are selected for treatment. In some instances, autonomously functioning thyroid nodules (AFTN) can be addressed with RFA. Depending on the proportion of cystic and solid components within a nodule, aspiration of the cystic component is recommended prior to ablation of the solid component. Therefore, for mixed nodules, a combination of PEIT and RFA is often done either simultaneously in the same setting or in two stages [35]. Primary thyroid cancer is not usually an indication for RFA. However, if a patient refuses or is unfit for surgery, RFA utilization can be considered. Monopolar electrode RFA is generally not recommended for pregnant women and patients with implanted electronic devices, such as a cardiac pacemaker [36].

Preoperative Evaluation and Preparation

Like HIFU, the target nodule is assessed both clinically by palpation and sonographically by US. Symptom severity and cosmetic concerns are assessed by VAS. Thyroid function tests are checked before ablation.

RFA

In contrast to HIFU, RFA is normally done without intravenous sedation or analgesia. The most effective approach to pain control during RFA treatment is the infiltration of local anesthesia superficially to the thyroid capsule, in the space between the nodule and strap muscles. Avoiding general anesthesia facilitates the recognition of problems or complications during treatment.

The most popular method for inserting the RFA needle into the target nodule is the trans-isthmic approach. In the trans-isthmic approach, under US guidance, the needle electrode is introduced into the isthmus and is then directed toward the lateral aspect of the gland. There are several benefits to this approach. First, the entire length of the electrode can be clearly visualized on US. Second, due to the angle at which it is introduced, the tip of the electrode is located far away from tracheoesophageal groove. This helps to minimize the risk of thermal injury to the recurrent laryngeal nerve. Finally, with this technique, a significant amount of surrounding thyroid parenchyma holds the electrode in place. This acts to stabilize it during swallowing and prevents the leakage of heated fluid from the nodule [29].

Moving Shot Technique

Unlike other clinical scenarios that are optimally ablated using the "fixed electrode" technique, RFA ablation of thyroid nodules is best achieved using the "moving shot" technique [37]. In the "moving shot" technique, the target nodule is abstractly divided into multiple, small ablation units. Each unit is then targeted separately, and the needle is moved from one unit to another until the entire volume of the nodule has been ablated (Fig. 6.3).

Efficacy of RFA Ablation

Kim et al. published one of the first series on RFA ablation of thyroid nodules [34]. They reported an overall shrinkage rate of 33–58% in the first month, 50–88% at 6 months, 79–90% at 2 years after treatment, and up to 93% at 4 years. Similar rates

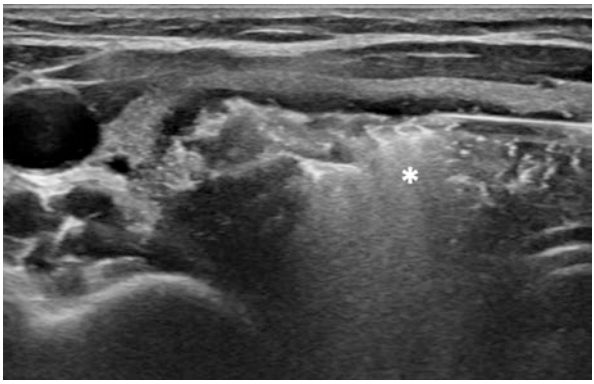

Fig. 6.3 Transverse image of a right thyroid nodule during thyroid radiofrequency ablation (RFA). Please note the position of the needle and hyper-echogenic changes from the ablation

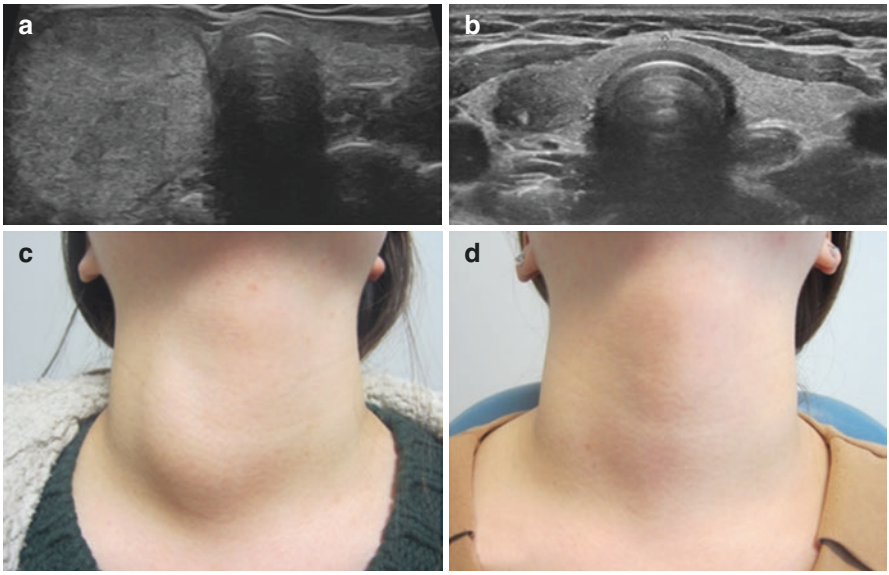

Fig. 6.4 Before (**a**, **c**) and after (**b**, **d**) images of thyroid radiofrequency ablation (RFA). Three sessions of RFA had been performed to 22.04 mL-volume right benign thyroid nodule (**a**). After 26 months, volume of the treated nodule became 1.55 mL (**b**). Cosmetic symptom subsided

were later confirmed by others [38]. For mixed cystic and solid nodules, it seems reasonable to use a combination of RFA and PEIT to complement each other [36].

In a 4-year study, the rate of nodule recurrence was reported to be 5.6%, and the major cause for these recurrences was the regrowth of undertreated tissue at the margins of nodules [39]. Therefore, it is clearly important to achieve a complete ablation of the entire nodule. However, this is not always feasible in one treatment session because of the crucial structures located close to the margin of the thyroid gland. Therefore, staged procedures can be considered to obtain maximum efficacy (Fig. 6.4) [39].

Apart from size, the location and composition of the nodule can influence the treatment efficacy. For example, nodules in the lower part of the thyroid gland are generally more difficult and less responsive to ablation simply because the sternum and clavicles can obscure the sonographic views of the nodule, making optimal needle placement difficult. On the other hand, nodules located far from the tracheo-esophageal groove are good lesions for RFA because the thermal area is far from the danger area where the recurrent laryngeal nerve is located. It has been noted that nodules having a greater cystic component tend to be more responsive to treatment than pure, solid isoechoic nodules, irrespective of size.

Although the efficacy of RFA for AFTNs can be variable, small, toxic nodules tend to respond well to treatment [40]. It appears that treating AFTNs in this manner requires ablation of the whole nodule in order to avoid the possibility of persistent hyperthyroidism.

Safety of RFA

RFA is a well-tolerated procedure with a low incidence of complications. A recent meta-analysis reported an overall complication rate of 2.11% in the treatment of benign thyroid nodules [41, 42]. Complications related to RFA can be classified into major and minor. Commonly encountered minor complications include pain (sense of heat or referred pain) during the procedure, neck hematoma, skin burn, edema, cough, and vomiting. Voice change (transient or permanent) is the most common major complication, and its overall incidence was 1.44%. Nodule rupture (0.17%), permanent hypothyroidism, and brachial plexus injury have also been reported in the literature [42, 43].

Since complications are a result of thermal injury to surrounding tissue, careful study of the ultrasonographic anatomy and accurate handling of the needle electrode inside the nodule are essential. The experience of the operator in RFA appears to be more important than that of HIFU. For RFA, to minimize thermal injury, a safe distance of at least 3 mm between the electrode and surrounding structures should be maintained during the ablation [41]. A hydrodissection technique (in which 5% dextrose is injected between the target nodule and adjacent structures) appears to be effective in minimizing thermal injury [42]. When ablating close to pain-sensitive structures, a cold dextrose solution can be injected directly to obtain rapid symptom relief [44, 45].

Discussion

Ablation techniques for thyroid nodule management have several distinct benefits over conventional treatment (i.e., thyroid surgery). First, it is organ preserving. Very few patients require thyroid hormone supplementation after ablation treatment,

while with surgery, this occurs quite frequently. Second, it does not result in a wound or scar after treatment. Therefore, it is perceived to be less invasive than surgery. Third, there is no need for general anesthesia or hospitalization. Patients can be managed on an ambulatory basis with these approaches. Despite these advantages, HIFU or RFA should not be considered as a true replacement or alternative to surgery because ultimately they merely reduce, not eliminate, thyroid nodules.

While HIFU can be considered to be totally noninvasive as compared to RFA, there are several shortcomings of HIFU, which are worth highlighting. First, HIFU ablation is more effective in smaller-sized nodules. For larger-sized (>15–20 mL) nodules, multiple or sequential treatment is often required [22]. Second, compared to RFA, it takes a longer time to ablate a similar area of thyroid tissue with HIFU. This is because the delivery of energy through the skin and subcutaneous tissues makes it less efficient. On average, using the current US-guided HIFU device, a well-selected 3 cm thyroid nodule would take approximately 45–60 minutes to completely ablate. With RFA, the same nodule would take only approximately 25–30 minutes to treat (Table 6.3). Although it is possible to shorten the treatment periods with HIFU by either increasing the power settings or shortening the required cooling periods, for safety reasons, this is not recommended. Third, the efficacy of ablation with HIFU remains highly unpredictable, with some nodules

Table 6.3 A comparison between different thermal techniques for benign thyroid nodules

Thermal technique	Cost[a]	Treatment duration	Main usage
PEIT	USD 50–100	5–10 minutes	Predominantly cystic benign thyroid nodules
RFA	Equipment: USD 25000 Consumables: USD600 per session	~15–30 minutes	Solid functioning benign thyroid nodules
LAT	Equipment with built-in laser source: ~ USD 12000 Nd/YAG laser source: ~USD 15,000–20,000 Consumables: ~USD 500 per session	~30 minutes	Cold nodules, autonomously functioning thyroid nodules and cysts
Microwave ablation	Equipment: USD 35000 Consumables: USD 400 per session	~25–30 minutes	Predominantly solid or solid benign nodules
HIFU	Equipment cost: ~USD 400,000 Annual maintenance: 10% of the base price Consumables: ~USD 350 per treatment	~45–60 minutes	Predominantly solid or solid benign nodules

Abbreviations: *PEIT* percutaneous ethanol injection therapy, *RFA* radiofrequency ablation, *LAT* laser ablation therapy, *HIFU* high-intensity focused ultrasound

[a]This can vary significantly between different institutions and countries

showing a better response than others. Finally, RFA allows for most nodules to be addressed. In contrast, HIFU can manage only a limited range of nodules, as deeper or more posteriorly located nodules are currently not treatable with this technology.

Conclusion

Local thermal ablation of benign thyroid nodules with HIFU and RFA appears to be a safe and effective treatment alternative for patients who are either unwilling or unfit to undergo conventional thyroid surgery. However, a large-scale, prospective trial with longer follow-up periods is required to evaluate the long-term outcomes of the various techniques. While HIFU and RFA both appear to be effective, future improvements in technology and techniques will be required to overcome some of their current limitations.

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Part II
Diagnosis and Preoperative Work-up of Parathyroid Disease

Chapter 7
Localization Studies for Hyperparathyroidism

Steven Craig, Adrian Harvey, and Janice L. Pasieka

Introduction

Preoperative localization of the parathyroid glands in primary hyperparathyroidism (HPT) can provide valuable information that can inform the nature and extent of parathyroid operations. Preoperative imaging studies are not diagnostic, and the indication for any imaging modality is solely for surgical planning. Although there are some general patterns of use of localization studies, parathyroid imaging techniques continue to improve, and their utilization, therefore, continues to evolve. At present, there is no imaging modality that is widely accepted as the gold standard, and the place of new techniques remains to be defined. In order to apply imaging techniques and protocols appropriately, it is imperative that parathyroid surgeons appreciate the advantages, limitations, accessibility, and nuances of the various imaging technologies available. Such an understanding will enable surgeons to develop evidence-based imaging algorithms for surgical planning that are tailored to locally available technology and expertise.

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M. C. Singer, D. J. Terris (eds.), *Innovations in Modern Endocrine Surgery*,
https://doi.org/10.1007/978-3-030-73951-5_7

Historical Perspectives on Parathyroid Localization

The surgical management of HPT has swung back and forth between bilateral neck exploration (BNE) and more focused approaches over the past century. The earliest parathyroid operations were neck explorations that were terminated once a single abnormal gland was found. It was only the subsequent observation of recurrences within these early series that leads to the realization of multi-gland disease as an entity, ushering in an era of standard four-gland explorations [1]. The early pioneers of parathyroid surgery, lacking access to reliable preoperative localization or intraoperative functional tests, depended solely on the morphological identification of the parathyroid glands to identify the source of hyperparathyroidism. In 1965, Dr. Oliver Cope, one of the founding figures of parathyroid surgery, insightfully ruminated about what the future might hold for the treatment of hyperparathyroidism:

> Next we shall have to find a better way to differentiate the neoplasm from the hyperplasia. Shall we always need to operate to do this, or could we observe something that would give a clue to how to tell before hand? [1]

By the mid-1960s, a BNE by an experienced surgeon was considered sufficient to distinguish multi-gland disease (MGD) from solitary adenoma. In the early 1980s, Tibblen [2] and Wang [3] championed a more focused approach since the majority of patients with HPT (80%–85%) had solitary adenomatous disease. Their work led to a unilateral approach whereby if on the first side explored one normal and one abnormal gland was found the procedure was terminated. Following these principles leads to a cure rate of 95% [3]; however, conversion to a BNE was needed 50% of the time as there was no way to predict preoperatively the side of the adenoma. This limited approach was not universally adopted by surgeons as it required significant experience and expertise to confidently make the decision to terminate the operation based on the morphological assessment of only two glands.

In subsequent decades, two significant developments occurred that offered the opportunity to differentiate solitary parathyroid adenomas from MGD and hence revolutionize the management of HPT: (1) radiologic techniques allowed for the preoperative detection of the possible location of diseased glands, and (2) rapid intraoperative parathyroid hormone (ioPTH) measurements helped to verify the success of surgical resection of all autonomous parathyroid tissue [4]. The advancements in imaging and hormone measurement allowed surgeons to develop and readopt more focused approaches such as image-directed [5] or unilateral explorations [6]. The rationale for targeted procedures is that the majority of patients with primary HPT have a single adenoma (>80–85%), and if a single adenoma can be reliably identified, it can be directly targeted and removed with a less extensive dissection, potentially resulting in decreased morbidity and operative time.

As preoperative localization techniques such as ultrasound and sestamibi improved, the adoption of focused techniques predictably increased [7]. This was particularly so in the setting of concordant imaging, where the overall success of focused approaches was reported to be >95% [8], and when the operation was supported by rapid ioPTH assays. Targeted parathyroid operations with accurate

preoperative imaging and ioPTH monitoring initially demonstrated cure rates comparable to those undergoing a bilateral neck exploration [9]. However, 10-year follow-up data from some series has subsequently shown higher late recurrence rates following a focused approach compared to a BNE [10, 11]. In some centers, image-directed approaches were entirely abandoned in favor of BNE [11]. However, many surgeons still successfully employ focal and unilateral approaches in appropriately selected patients.

The Role of Imaging in Parathyroid Surgery

Parathyroid imaging has no role in confirming or excluding the diagnosis of HPT. Additionally, it should not be used to select patients for surgical referral. Optimally, imaging should only be considered *after* the decision to pursue surgical management for HPT has been made. Imaging studies in parathyroid surgery are an adjunct that (1) can help guide surgical planning and (2) exclude concomitant thyroid pathology [12]. The optimal surgical approach depends on (1) surgeon experience and practice pattern, (2) the localization of abnormal parathyroids (in eutopic or ectopic positions), (3) the concordance of imaging results, (4) the level of suspicion for multi-gland disease (MGD), and (5) whether the patient has had prior neck surgery or has recurrent HPT. When advanced imaging techniques are not available, or not cost-effective, a BNE performed by an experienced parathyroid surgeon remains an entirely appropriate operative approach that is both safe and highly effective [13, 14]. Localization studies for HPT can be grouped into anatomical imaging modalities, functional imaging modalities, and invasive techniques.

Anatomical Imaging Modalities

Ultrasonography

Description of Technology and Technique

Ultrasound imaging utilizes ultrasound waves to detect interfaces between tissues of different density/acoustic impedance, which can then be converted into a two-dimensional image. In parathyroid imaging, this is typically done using B-mode scanning with a high-frequency linear probe. The patient is positioned supine with the neck extended. Scanning is first performed in the axial plane from the level of the carotid bifurcation/hyoid bone down to the thoracic inlet. Angulation of the probe at the bony boundary of the thoracic inlet allows limited visualization of the superior mediastinum. Scanning is then performed in the sagittal plane from the jugular vein laterally to the thyroid isthmus and trachea medially.

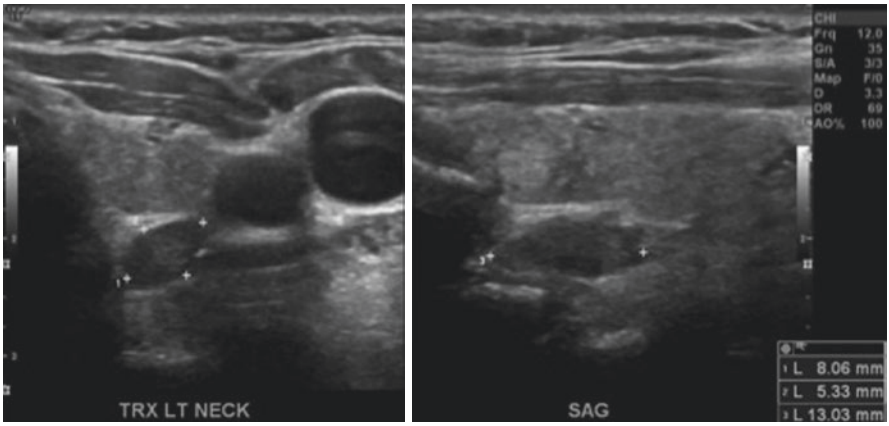

Fig. 7.1 Characteristic appearance of a parathyroid adenoma on ultrasound. A typical appearance of a parathyroid adenoma on ultrasound imaging demonstrating a hypoechoic, ovoid structure located deep to the thyroid lobe and medial to the carotid artery and jugular vein (the so-called three circle sign). The gland can be clearly seen in both the axial and sagittal planes. A slightly echogenic capsule can also be seen at the interface between the thyroid and parathyroid glands

It is important to note that normal parathyroid glands are not seen on ultrasound imaging. However, on standard grayscale images, abnormal parathyroid glands typically appear as ovoid masses that are hypoechoic when compared to adjacent thyroid tissue. They may also have an echogenic capsule, particularly at the interface between the thyroid and an enlarged parathyroid gland (Fig. 7.1). As adenomas enlarge, they may become lobulated, cystic, fibrotic, calcified, or hemorrhagic. Thus, particularly in larger adenomas and long-standing severe HPT, cystic degeneration or hemorrhage may induce areas of fat deposition, calcification, and fibrosis which renders a gland heterogenous and in some places hyperechoic [15].

Color or power Doppler modes can also be used as sonographic adjuncts to demonstrate vascular patterns that help to differentiate parathyroid adenomas from enlarged lymph nodes or thyroid nodules. In Doppler imaging, parathyroid adenomas are described as often having internal vascularity and an enlarged extra-thyroidal feeding vessel. A peripheral arc or rim of vascularity due to branching of this feeding vessel around the periphery before it enters the gland is also its characteristic [16–18]. In addition, determining where feeding vessels enter a lesion can help to differentiate between parathyroid glands and lymph nodes: in parathyroid glands, they enter at the end of the enlarged gland (sometimes termed a "polar vessel"), whereas in lymph nodes, the supplying vessels enter at the hilum rather than the pole [19].

The reported sensitivity and specificity of ultrasound in detecting diseased parathyroid glands are variable. This is not unexpected given that ultrasound is an operator-dependent technology and that in certain anatomical locations (such as behind the pharynx where air prevents the transmission of sound waves and deep to the sternum where sound waves cannot penetrate), adenomas are difficult to detect. A meta-analysis of studies investigating the accuracy of ultrasound in primary HPT

reported a pooled estimate of sensitivity of 76.1% (95% CI 70.4–81.4%) and a positive predictive value of 93.2% (95% CI 90.7–95.3%) [20]. The sensitivity of ultrasound is, however, significantly lower in the setting of multi-gland disease [21]. It has also been reported that surgeon-performed ultrasound has as higher sensitivity than radiologist-performed ultrasound (82% vs 42%, respectively) [22]. Critically, aside from detecting abnormal parathyroid glands, US permits concurrent assessment of any thyroid abnormalities, which is important for appropriate surgical planning. In patients presenting with HPT, concurrent thyroid nodules are seen in up to 57% of patients, and concurrent thyroid malignancy has been reported in 6% of patients [23]. The relative advantages and disadvantages of this technology are shown in Table 7.1.

Table 7.1 Comparison of imaging modalities for parathyroid localization

	Ultrasound	Sestamibi	4D-CT	MRI
Accessibility	Easily accessible, can be used at bedside, in office, or in OR	Dependent on presence of nuclear medicine department	CT scanners becoming more widely available	Limited availability for parathyroid disease
Cost (69)	Most cost-effective single modality	Least cost-effective single modality	Less cost-effective than US but more cost-effective than sestamibi	Significantly higher cost than other modalities
Pooled estimate of sensitivity and PPV (20)	Sens: 76.1% (95% CI 70.4–81.4%) PPV: 93.2% (95% CI 90.7–95.3%)	Sens: 78.9% (95% CI 64.0–90.6%) PPV: 90.7% (95% CI 83.5–96.0%)	Sens: 89.4%[a] PPV: 93.5%[a]	N/A
Advantages	No radiation Can detect concomitant thyroid pathology Can assess vocal cords Noninvasive and well tolerated	Lower radiation dose than 4D-CT Improved detection of mediastinal and retropharyngeal glands compared to US	Greatest anatomical detail May be more sensitive in MGD and for small glands Improved detection of mediastinal and retropharyngeal glands compared to US	No radiation No contrast exposure No other added advantages over 4D-CT
Disadvantages	Operator dependent Decreased performance in obese and in concurrent thyroid pathology Difficult to visualize mediastinum and retropharyngeal areas	More time-consuming and position dependent than US and CT Requires small radiation dose Less reliable in setting of MGD Does not adequately assess the thyroid	Requires specialist protocols and interpretation Highest radiation exposure Requires contrast Does not adequately assess the thyroid	Time-consuming Motion artefact can significantly distort results

[a]Weighted average due to insufficient number of studies in cited meta-analysis

There are a number of sonographic innovations that have been proposed to increase the value of preoperative ultrasound. Ultrasound elastography is a noninvasive technique that measures tissue displacement to quantify its elasticity and stiffness. A number of studies have suggested that these mechanical characteristics can be useful adjuncts to differentiate parathyroid adenomas, based on the understanding that adenomas have greater stiffness than parathyroid hyperplasia and benign thyroid tissue but less stiffness than malignant nodules [24–27]. A shear wave velocity cutoff of 1.72–1.73 m/s has been reported in small series [24, 26], to be able to differentiate between parathyroid adenomas and thyroid tissue. However, more comprehensive studies are required to determine if the application of ultrasound elastography has a clinically significant benefit. Other sonographic adjuncts include three-dimensional ultrasonography, which is reported to have significantly higher sensitivity than two-dimensional ultrasonography for localization of smaller glands [28], and contrast-enhanced ultrasonography, which is suggested to achieve a higher sensitivity compared to conventional ultrasonography in some series [29–31], but not others [32].

Four-Dimensional Computed Tomography

Conventional CT scanning has not been shown to be useful in parathyroid localization. However, the advent of multiphase CT scanning, also known as four-dimensional computed tomography (4D-CT), has established a potential role in the localization of parathyroid glands. 4D-CT is so named because it adds an additional dimension, specifically the differential pattern of contrast enhancement over time, to images in a three-dimensional data set (axial, sagittal, and coronal). The principle of this technology is that thyroid, parathyroid, and lymphatic tissues display distinct contrast enhancement patterns over time. For example, the typical finding of a parathyroid adenoma is of a low-attenuation soft tissue mass on non-contrast phase, with brisk enhancement in the arterial phase and rapid washout in the delayed phase (Fig. 7.2). In contrast, lymph nodes demonstrate progressive contrast enhancement with the peak in the delayed phase.

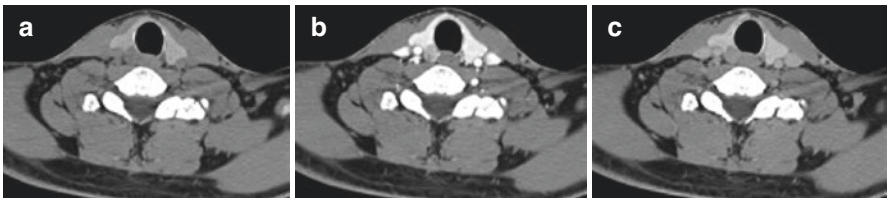

Fig. 7.2 Characteristic appearance of a parathyroid adenoma on 4D-CT. A typical appearance of a parathyroid adenoma on 4D-CT. On non-contrast images (**a**), an elongated nodule is seen in the tracheoesophageal groove that is *hypodense* relative to normal thyroid parenchyma. It enhances during the arterial phase (**b**), though less than normal adjacent thyroid parenchyma. On venous phase images (**c**), the nodule washes out and enhances less than normal thyroid parenchyma. This pattern is characteristic of a parathyroid adenoma

Since the original description of 4D-CT, for parathyroid localization in 2006 [33], a number of modified scanning protocols have been produced. Some institutions interpret "four-dimensions" to mean "four-phases": one non-contrast phase and three contrast-enhanced phases [34–37]. At other institutions, "two-phase" scanning protocols have been developed [38–40]. It is unclear which scanning protocol, if any, is superior for parathyroid gland detection. Furthermore, it is difficult to make comparison of outcomes published in the literature due to differences in scanning and interpretation protocols across institutions. However, multiple institutions have reported a high sensitivity and positive predictive value with their experiences [35–37, 41]. In meta-analyses and direct comparisons, 4D-CT has been reported to have superior sensitivity and positive predictive value when compared to ultrasound and nuclear scintigraphy [20, 33, 36, 42]. Although the sensitivity of 4D-CT is decreased in multi-gland disease, it does appear that it remains superior to the sensitivity of ultrasound and nuclear scintigraphy in direct comparisons [33, 41]. In one study, 4D-CT correctly identified multi-gland disease in 85% of patients, in contrast to ultrasound and sestamibi which were unable to detect multi-gland disease in any of the same patients [36]. Furthermore, 4D-CT is reported to offer improved localization in re-operative scenarios [43].

Despite the reported superior sensitivity of 4D-CT, its role in preoperative localization is variable. An international survey of 361 radiologists found 55% of radiologists have used 4D-CT in their practice for parathyroid localization. Of these, 10% used 4D-CT as a first-line investigation, 13% used 4D-CT routinely in combination with ultrasound and/or scintigraphy, and 76% employed 4D-CT as a second-line option [44].

There have been two recent innovations that attempt to reduce the limitations of 4D-CT. First, different groups have developed protocols with reduced imaging phases in an effort to minimize radiation exposure while still maintaining diagnostic accuracy [38–40]. One study even proposed that a single arterial phase may be adequate [45]. These approaches have been questioned by other investigators, who cite that approximately 25% of adenomas have similar enhancement to thyroid on arterial and delayed phases, and could therefore be missed without the benefit of a non-contrast phase [46]. Further research is required to determine the optimal balance of diagnostic accuracy and radiation exposure. A second suggested enhancement to 4D-CT is the use of predictive scoring systems, which have been developed and prospectively validated, to identify patients with a high likelihood of multi-gland disease [47, 48]. Sho et al. analyzed two 4D-CT scoring systems in a prospectively accrued cohort: the "Composite multi-gland disease score" which is calculated from the 4D-CT findings and the Wisconsin Index (a product of parathyroid hormone and calcium levels) and the "4D-CT multi-gland disease score" which is derived from 4D-CT, images alone [48]. They reported that in a cohort of 71 patients, a *Composite multi-gland disease score* of 6 was 100% specific for multi-gland disease, while in the *4D-CT multi-gland disease* system, a score of 4 was 88% specific for multi-gland disease. 4D-CT and multi-gland scoring systems may therefore offer a benefit in surgical planning for patient populations at higher risk of multi-gland, such as younger patients.

Magnetic Resonance Imaging

Although magnetic resonance imaging (MRI) can provide highly detailed anatomical images without radiation exposure or the need for radiotracers and contrast materials, it is rarely employed as a primary localization technique for parathyroid disease. This has largely been due to a generally lower, although highly variable, reported sensitivity range (43%–94%) [49–52]. As in other modalities, variation in MRI protocols may account for some of the difference in sensitivities between studies. In addition, the increased cost and reduced accessibility of MRI limit its use. As with CT, the addition of dynamic contrast-enhanced imaging protocols has been reported to greatly improve the diagnostic accuracy of MRI technology for parathyroid localization [53]. An interesting advantage of MRI contrast enhancement is that image acquisition is continuous during and after contrast administration, which allows for the quantification of perfusion parameters such as time to peak, wash in, and washout. The addition of contrast media negates one of main indications for MRI, however, as MRI is currently often only considered for patients who have contraindications to contrast media or radiation exposure. MRI may also have a role in re-operative cases when other imaging studies are negative [54].

Functional Imaging Modalities

Nuclear Scintigraphy

The detection of abnormal parathyroid glands on nuclear scintigraphy depends on the focal uptake and prolonged retention of radionuclide tracer in hyperfunctional parathyroid tissue. The most common radiotracer employed in parathyroid scintigraphy is ^{99m}Tc-sestamibi, which is concentrated in the mitochondria of various metabolically active tissues including the myocardium and thyroid and parathyroid glands. Because radiotracer concentrates in both thyroid and parathyroid tissues, scintigraphic scanning protocols have been developed to distinguish the two tissues by using either a single isotope in dual phases or dual isotopes in a single phase.

Dual-isotope/single-phase studies were first introduced in the 1970s using thallium and pertechnetate radionuclides. Because both ^{201}TI-thallium and ^{99m}Tc-pertechnetate are taken up by thyroid tissue but only ^{201}TI-thallium is taken up by abnormal parathyroid tissue, a subtraction scanning protocol was developed. ^{201}TI-Thallium and ^{99m}Tc-pertechnetate images are obtained separately but without moving the patient, and a subtraction image is then generated. In the 1990s, the introduction of ^{99m}Tc-sestamibi allowed for the development of single-isotope/dual-phase study protocols. In these protocols, ^{99m}Tc-sestamibi is taken up by both the thyroid and parathyroid gland but washes out from abnormal parathyroid tissue at a much slower rate than normal thyroid tissue, allowing for differentiation by observing activity washout of surrounding tissue on delayed imaging.

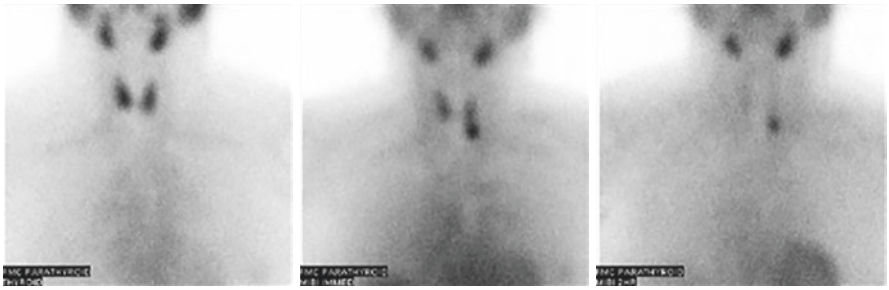

Fig. 7.3 Characteristic appearance of a parathyroid adenoma on sestamibi. On the left thyroid image, uniform distribution of pertechnetate is seen in both lobes. In the middle image immediately after sestamibi injection, radiotracer is seen in the distribution of the thyroid gland, though there is a subtle elongation of the left inferior pole. On the right image at a two-hour delay, persistent radiotracer activity is seen at the inferior margin of the left lobe, consistent with a left inferior parathyroid adenoma

The use of different radiotracers and imaging protocols makes evaluation and comparison of the efficacy of planar nuclear scintigraphy difficult. For example, in one meta-analysis of planar parathyroid scintigraphy, the authors found that reported sensitivities across 52 studies ranged from 39% to 92% [55]. Other studies have also reported reduced sensitivity of scintigraphy in smaller glands [56] and in multigland disease [21]. Nonetheless, planar nuclear scintigraphy is one of the most commonly employed modalities that offers a number of distinct advantages (Table 7.1).

An important relative limitation of nuclear scintigraphy is its poor performance in the setting of MGD, and as such, it is not commonly utilized in patients with known MGD (i.e., patients with tertiary HPT or MEN1 patients). In MGD, ^{99m}Tc-sestamibi scan will show no localization in a third of patients and correctly demonstrate MGD in an additional third. Unfortunately, it can also be misleading in up to one-third of patients by demonstrating a single focus of uptake. In patients suspected of having MGD, anatomical imaging is likely to be more useful than functional imaging (Fig. 7.3) [57].

SPECT/SPECT-CT

More recently, single-photon emission computed tomography (SPECT) and SPECT-CT protocols were developed to try to improve parathyroid localization by adding anatomical information to conventional scintigraphy. SPECT imaging is performed by taking multiple, two-dimensional scintigraphic projections from different angles, which then undergo a computed tomographic reconstruction to yield a three-dimensional data set. In SPECT-CT, the SPECT images are registered with conventional grayscale CT images to provide an additional layer of anatomical detail but at the cost of additional ionizing radiation exposure. A meta-analysis of sestamibi-SPECT imaging found a sensitivity and positive predictive value of

78.9% (95% CI 64–90.6%) and 90.7% (95% CI 83.5–96%), which is similar in performance to that reported for ultrasonography. Another recent meta-analysis reports that the addition of SPECT-CT imaging improves the performance of scintigraphy when compared with planar and SPECT imaging alone, with reported sensitivities of 86% for SPECT-CT, 74% for SPECT, and 70% for planar techniques [58]. SPECT-CT is also reported to be superior to SPECT and planar imaging for detection for ectopic parathyroid adenomas [58].

PET/CT

The most recent innovation in nuclear scintigraphy for parathyroid diagnostic imaging has been the development of novel radiopharmaceuticals, such as ^{18}F-fluorcholine and ^{11}C-methionine, for use in positron emission tomography/computed tomography (PET/CT). ^{11}C-methionine was the most extensively studied initially, but this radiopharmaceutical is also taken up by the thyroid which has limited its utility, with a pooled sensitivity estimate of only 69% [59]. ^{18}F-Fluorcholine is emerging as a more promising radiopharmaceutical for use with PET technology. In a recent prospective study, ^{18}F-fluorcholine PET/CT showed clear superiority to SPECT/CT in the detection of parathyroid adenomas, particularly in smaller glands [60]. The excellent diagnostic performance of choline-based PET imaging was also shown in a 2019 meta-analysis which reported per-patient sensitivity of 95% (95% CI 92–97%) and positive predictive value of 97% (95% CI 95–98%). The additional diagnostic value of ^{18}F-fluorcholine PET imaging in HPT with negative or discordant imaging results has been reported to be high in small series, with parathyroid detection rates of 94–96% [61, 62]. Although expense, radiation, and availability may restrict the utility of PET/CT in HPT, it may find a role as a second-line modality for re-operative cases, particularly those with discordant or negative imaging. However, at the present time, this compound is not yet FDA-approved.

Invasive Techniques

The use of invasive techniques is largely reserved for difficult re-operative cases in which noninvasive imaging has inadequately localized the source of recurrent disease.

Fine-Needle Aspiration Biopsy

Fine-needle aspiration (FNA) biopsy can be used to confirm potential parathyroid glands that are suspected on imaging. If a suspected parathyroid adenoma has characteristics of both thyroid and parathyroid tissue, for example, in the setting of an

intrathyroidal parathyroid, an FNA of the lesion can be taken under ultrasound guidance and the aspirate measured for intact parathyroid hormone (PTH). Parathyroid FNA has been reported to have a high sensitivity in properly selected patients [63, 64]. However, this technique is dependent on the ability to correctly localize a potential target with ultrasound and enter it with a percutaneous needle. Additionally, as this is an invasive technique, clinicians should consider that complications such as parathyromatosis, parathyroid abscess, and neck hematoma, although rare, have been reported [12, 63]. These complications, as well as the scarring that can sometimes occur after FNA, have the potential to make any future surgery more difficult, and as such, this modality is rarely employed preoperatively and should only be used if the result would change the course of management.

Selective Venous Sampling and Selective Arteriography

Selective venous sampling is an invasive technique that obtains blood specimens for PTH-level measurement from select points of the thyroid, jugular, and brachiocephalic venous systems. This process attempts to localize the venous tributary that drains the hyperfunctioning gland and hence guide surgery [65]. On meta-analysis, the reported sensitivity of this technique to correctly lateralize the side of the hyperfunctional parathyroid tissue is 74% [66]. Selective arteriography utilizes contrast media and the hypervascular nature of abnormal parathyroid glands to attempt to identify their location. Contrast is infused, via a trans-arterial catheter, into or adjacent to the thyrocervical trunk. As with FNA, the invasive nature of selective venous sampling and selective arteriography, their potential to cause vascular complications, and the high degree of expertise required to perform them correctly severely limit their applicability. These invasive modalities should be reserved only for exceptional remedial cases and be undertaken at centers with significant experience in their performance. Given the arterial instrumentation in selective arteriography, it carries an additional risk of stroke. Consequently, although it is advocated by some as a valuable technique in patients with extensive prior neck surgery (in which the anatomy and perfusion may be significantly altered) [67, 68], it is rarely used.

Choice of Imaging Modalities

The choice of imaging algorithm is dependent on the anticipated approach (BNE vs a more focused approach), quality and availability of imaging technology, local experience and expertise, accessibility of intraoperative adjuncts (such as intraoperative PTH testing), and cost-effectiveness. While the data regarding the performance of each imaging modality is important, perhaps equally significant is the information each test provides and how the surgeon might apply the results in their

practice. In addition, surgeons should consider the limitations and contraindications of each modality.

The combination of ultrasonography and nuclear scintigraphy has traditionally been favored, based on the finding that combining these functional and anatomical modalities significantly improves the sensitivity over either technique alone [8, 13]. The reported efficacy of 4D-CT has broadened the use of this modality, including as a first-line and stand-alone investigation [44]. Ultrasonography is the most cost-effective single modality and provides information about any coexisting thyroid pathology [69]. Information about coexisting thyroid pathology is invaluable to surgeons as all suspicious thyroid nodules should be evaluated prior to parathyroidectomy, as the surgical approach to parathyroid disease may change if the thyroid gland also requires surgical attention [12]. Sestamibi-SPECT combined with ultrasound, and in discordant cases the addition of 4D-CT, has been reported to be the most cost-effective imaging algorithm [69], mostly because improved localization appears to result in the need for fewer bilateral explorations. The cost-effectiveness of 4D-CT scanning algorithms requires further investigation, particularly given its growing acceptance.

Re-operative parathyroid surgery is a unique and challenging scenario as it carries an increased risk of surgical morbidity [70] and lower chance of therapeutic success [71]. As such, successful localization is particularly important in these cases as it permits a more focused approach that may reduce the risk of nerve injury and hypoparathyroidism. However, it should be recognized that preoperative localization studies form only part of the clinical evaluation for re-operative cases, which must include confirmation of the biochemical diagnosis of persistent or recurrent HPT, a thorough assessment of any prior localization studies, review of the initial operative notes and/or discussion with the initial surgeon, and review of ioPTH and histopathology results if available. A common approach in re-operative parathyroid localization is to sequentially obtain imaging studies until concordance is obtained. If no apparent targets emerge with noninvasive studies, further investigation with invasive techniques can then be considered [72]. It has been reported though that improvements in preoperative imaging have decreased the need of invasive tests in re-operative scenarios [73]. As with cases of primary surgery, in the re-operative setting, the order in which localization studies are obtained depends on availability and local expertise, as well as an understanding of how the information obtained would affect the surgical approach [74, 75].

Conclusion

Preoperative imaging in HPT has drastically improved since the days when Professor John Doppman made the classic statement “the only localization study indicated in a patient with untreated hyperparathyroidism is the localization of an experienced surgeon” [76]. However, imaging should not be pursued indiscriminately, but rather should be utilized for surgical planning in appropriate patients

with a confirmed diagnosis of HPT. Parathyroid imaging techniques are adjuncts for the operating surgeon; it is the application of the limitations of these modalities to operative findings that has contributed to the excellent cure rates achieved in many centers.

Utilization of anatomical imaging, such as surgeon-directed ultrasound, has several advantages. In addition to being low cost, it can also provide information about concomitant thyroid pathology that can facilitate the planning of the optimal operation for HPT. Functional imaging, such as sestamibi scanning, can provide additional concordance in patients in whom a focused approach is considered. Newer modalities may eventually prove to be superior; however, until such time, the success of the primary operation still relies on the experience of the surgeon and his or her ability to interpret the information obtained from preoperative imaging studies within the context of the operative findings.

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Chapter 8
Subtle Variants of Hyperparathyroidism: Normohormonal Hyperparathyroidism

Julia E. Noel, David L. Steward, and Lisa A. Orloff

Introduction

Primary hyperparathyroidism (HPT) is a common disorder resulting from the excess release of parathyroid hormone (PTH) from one or more parathyroid glands. PTH functions to increase the serum calcium level by mobilizing stores from bone, sparing calcium from urinary excretion, and facilitating absorption in the small intestine. Inappropriate regulation of this hormone leads to hypercalcemia, the biochemical signature of primary HPT. Physical manifestations of disease can include fatigue, psychiatric or mood changes, nephrolithiasis, abdominal pain, musculoskeletal aches, and decreased bone mineral density. Increasing focus on bone health and the early detection of osteoporosis and osteopenia have led to more routine serologic testing and bone densitometry in the general population. As a result, HPT has been identified with increased incidence and, in many cases, with a subtle or non-classic biochemical profile. These situations can present significant challenges to managing physicians, as the diagnosis may be uncertain and management guidelines less applicable.

While normocalcemic hyperparathyroidism (NCHPT) is better described in the literature, less is known about the phenotype of hypercalcemia and normal intact

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M. C. Singer, D. J. Terris (eds.), *Innovations in Modern Endocrine Surgery*,
https://doi.org/10.1007/978-3-030-73951-5_8

PTH. This chapter describes in detail the entity of normohormonal hyperparathyroidism (NHHPT), a phenotype characterized by normal PTH levels with elevated serum calcium. Presentation, symptoms, biochemical interpretation, and imaging are reviewed. The nuances of diagnosis and management are discussed, as are intraoperative pitfalls and postoperative considerations.

Incidence and Etiology

The incidence of primary HPT saw a marked rise after the introduction of the multichannel autoanalyzer and automated serum calcium in the 1970s [1]. Recent investigations confirmed another dramatic increase in detection in the US population in the late 1990s, concomitant with the introduction of national osteoporosis screening guidelines and developing medical therapies [2, 3]. This trend had also been reported internationally in Asia and Europe [4, 5]. The second surge in diagnosis gave way to the recognition of "mild HPT," an incompletely defined term often used to encompass the subset of patients with a mixed biochemical presentation – those who are either normocalcemic with elevated PTH or hypercalcemic with normal but inappropriately non-suppressed PTH. It is estimated that these more subtle variants constitute 5–27% of patients with primary HPT [6–9]. The largest series of 388 patients with mild HPT reported a distribution of 31.4% with normocalcemic and 68.6% with normohormonal disease.

The first reported presentation of primary HPT with normal PTH came from Hollenberg and Arnold in 1991 in a man with back pain and musculoskeletal complaints, in whom a single adenoma was ultimately found. The authors surmised that the presence of circulating antibodies, PTH-related protein, an unmeasurable but overactive PTH molecule, or increased peripheral sensitivity to normal levels may have explained their observation [10]. A larger series published in 2011 reported a 5.5% incidence of normohormonal disease among all patients undergoing parathyroid exploration for primary HPT. This literature proposed that some patients may have lower PTH set points, anatomic barriers to peripheral PTH circulation, or labile values based upon external supplements and hormonal or biologic variations [6].

Several authors have suggested that mild HPT represents an early stage in the evolution to more classic disease. However, most studies have focused on normocalcemic HPT (NCHPT). Lowe et al. found that 41% of patients with normal serum calcium levels showed either biochemical or end-organ evidence of disease progression over a median of 3 years without surgical intervention [11]. Bilezikian and Silverberg reported similar results in a group with mild disease, 22% of whom developed overt hypercalcemia over 4 years of nonoperative management [12]. Finally, Lundgren et al. found that patients with normocalcemia had less extensive morphologic and functional abnormalities in histologic analysis of removed adenomatous glands, supporting the hypothesis of mild disease as a precursor to overt HPT [13].

Presentation

While it is during the screening for and workup of osteoporosis that the majority of patients with NCHPT are recognized, it is through routine serum calcium testing that the majority of patients with NHHPT are identified, most of whom are postmenopausal women [11]. In one series, 74% of patients with NHHPT presented after the incidental discovery of hypercalcemia on laboratory screening. However, the biochemically mild nature of the presentation did not necessarily correspond with symptomatology as compared with classic disease. Upon further evaluation, 70% of these patients had at least one symptom or sign of classical primary HPT – 50% had abnormal bone densitometry, 37% reported neuropsychiatric symptoms, and 17% had a history of nephrolithiasis [6].

Similarly, in a study of 18 patients with mild HPT (NCHPT and NHHPT), 50% presented with at least one symptom of nephrolithiasis, osteoporosis, fracture, or neuromuscular complaints, versus 43% of patients with classic HPT. In another series of 211 patients, 9% of whom had NHHPT and 12% with NCHPT, those with mild disease (encompassing both groups) exhibited twice the proportion of kidney stones and more fatigue than the classic group. Bone mineral density T scores were equivalent [9]. Amin et al. reported that 90% of normohormonal patients were symptomatic at presentation, 19% of whom had nephrolithiasis, 7% with fractures, 72% neurocognitive symptoms, and 70% with reduced bone mineral density [14]. Overall, the data indicates that the symptomatic profile of NHHPT is not significantly different from classic disease.

Biochemical Profile and Interpretation

The biochemical profile of NHHPT is tremendously variable and is perhaps the most challenging initial obstacle in making the diagnosis. In NHHPT, in the context of hypercalcemia, PTH values are more commonly at the high end of the normal reference range and readily recognized as inappropriately elevated or non-suppressed. Prior studies have demonstrated that average PTH values in NHHPT range between 47 and 62 pg/mL (with a reference range of 10–65 pg/mL) [6, 15–17]. However, caution and a high degree of suspicion must be employed to identify the subset of patients with unexpectedly low PTH levels. Wallace et al. reported a subgroup analysis of 46 NHHPT patients with histopathologically confirmed abnormal parathyroid glands with PTH levels <40 pg/mL, 2 of whom had values of 5 and 15 pg/mL, respectively [6]. Another large series reported maximum PTH values as low as 25–30 pg/mL and, in general, observed very poor correlation between serum PTH and calcium values in primary HPT [18]. The interpreting physician should, therefore, be cautious in eliminating NHHPT as a possible diagnosis simply because the PTH values do not appear at the high end of the normal range. Furthermore, strict

reliance on published serum calcium/PTH nomograms in identifying an inappropriate biochemical relationship may lead to the mistaken exclusion of this patient subset.

Some authors suggest that obtaining multiple PTH values may clarify the diagnosis. Assay variability and the potential inability of an assay to recognize the PTH molecule has led to the recommendation that the PTH in indeterminate cases be subsequently evaluated by other assays employing different antibodies [7]. The proceedings of the fourth international workshop on asymptomatic HPT more specifically address differences between the second- and third-generation PTH assays [19]. The second-generation assay, which is the intact PTH assay, recognizes the full PTH molecule (1–84) but also detects large circulating fragments. The third-generation assay has overcome this issue using a labeled antibody to be more specific to the whole 1–84 amino acid chain. Mean PTH concentrations with the third-generation assay are, therefore, typically lower than with the second-generation assay [19]. A study comparing a chemiluminescence immunoassay with immunoradiometric (IRMA) and enzyme-linked immunosorbent assays (ELISA) found that PTH values measured by IRMA and chemiluminescence were, on average, 50% and 30% lower, respectively, than the second-generation intact PTH measurement [20]. Even within the third-generation assays, however, detection methods may produce varying results. This same study showed that the chemiluminescence immunoassay yielded higher results than the IRMA and ELISA, which were comparable. The authors highlight the importance of using different reference intervals for each of the PTH assays [20].

Urine calcium excretion can be a critical aspect of primary HPT evaluation, both to confirm the diagnosis and to rule out the rare patient with familial hypocalciuric hypercalcemia (FHH), in which a 24-hour urinary calcium excretion and/or the fractional excretion of calcium is very low (<100 mg/24 h, or $FE_{Ca} < 1\%$). In two series of patients with NHHPT, the mean 24-hour urine calcium excretion was 316.1 and 323 mg/24 h. When comparing these values to patients with classic HPT, there was no significant difference in urinary calcium in either study [6, 15].

It is well known that hypovitaminosis D is more common in primary HPT than in the general population. This is perhaps due to the shorter half-life of serum 25(OH) vitamin D in hyperparathyroid states; however, the relationship between calcium and vitamin D is complex and incompletely understood. The observation of low vitamin D can sometimes be misleading and raise concern for a secondary HPT, though it is a more challenging confounder in the normocalcemic variant. A large series of 10,000 patients with primary HPT reported decreasing vitamin D values as serum calcium levels increased [18]. This corresponded with a decreased intraoperative finding of multigland parathyroid hyperplasia and greater incidence of single gland disease. [18]. The lack of association between vitamin D status and NHHPT was confirmed in another study comparing normohormonal and classic primary HPT [6].

Table 8.1 Differential diagnosis of hypercalcemia and maneuvers that may help clarify the most common causes

Diagnosis	Serum calcium	PTH	25 OH vitamin D	24 h urine Ca	Confirmation
Classic HPT	High	High	Normal[a]	High	Confirm via repeat labs
NHHPT	High	Normal/ high normal	Normal[a]	Normal/ high	Consider cinacalcet challenge if low PTH
Tertiary hyperparathyroidism	High/ normal	High	Low/ normal	Normal	History of ESRD with renal transplant
Malignancy/skeletal metastases	High	Low/ normal	Normal	Normal/ high	History of carcinoma, serum and urine electrophoresis, PET/CT, or radionuclide scan
Malignancy/ paraneoplastic syndrome	High	Low	Normal	Normal/ high	Elevated PTHrP
Familial hypocalciuric hypercalcemia	High	Normal/ high	Normal	Low	24-h urine Ca <100 or FECa <1%, consider calcium-sensing receptor (CaSR) mutation
Granulomatous disease (i.e., sarcoidosis)	High	Low/ normal	Normal/ high	Normal	Chest X-ray, serum ACE level, elevated 1–25(OH) vitamin D, TB testing
Thiazide diuretics	High	Low	Normal	Normal/ low	Hold or decrease medication as permissible, recheck labs
Excessive vitamin D or calcium supplementation	High	Low	High	Normal/ high	Hold supplementation, recheck level
Hyperthyroidism/ Graves' disease	High	Low	Normal	Normal/ high	Low TSH, elevated T3/ T4, presence of TSH receptor antibodies

[a]Vitamin D deficiency CAN coexist but should be corrected before assuming that the HPT diagnosis is correct

To further confirm the diagnosis of NHHPT, an oral cinacalcet challenge can be administered. While PTH levels may already be normal and show minimal change, serum calcium levels should drop from an elevated level into the normal range 1 hour after a single 60 mg oral dose of cinacalcet if the diagnosis of NHHPT is correct [21].

Finally, alternate causes of hypercalcemia must be considered and ruled out. While there are no specific recommendations for routine laboratory testing in this setting, the treating physician should assess if hypercalcemia may be attributable to malignancy, granulomatous disease, calcium-sensing receptor mutations, diuretics,

lithium, or excessive supplementation. Table 8.1 summarizes the differential diagnoses and maneuvers that may be pursued if there is suspicion for these alternate diagnoses.

Localization Studies

Preoperative localization imaging is a valuable adjunct in planning a surgical approach in primary HPT. Typically, patients will undergo some combination of 99mTc-Sestamibi scanning, ultrasonography, or 4D CT depending on institution protocols and surgeon preferences. While it is the role of localization studies to guide surgery and not to render a diagnosis of HPT, in mild or indeterminate cases, imaging results may in reality influence whether or not to offer surgical intervention. However, multiple studies have shown that preoperative localization in NHHPT is often less likely to reveal a target lesion as compared with classic disease. The physician must also keep in mind that all of these studies are susceptible to false-positive results, especially in the presence of central lymphadenopathy or thyroid nodules.

In an analysis of 44 patients with NHHPT, 35 (80%) localized on preoperative ultrasound, Sestamibi, or both, while the remaining 20% did not localize [6]. Of 916 patients with typical disease, 91% localized on at least one imaging modality [6]. Similarly, Mischis-Troussard et al. noted that cervical ultrasound demonstrated a candidate adenoma in only 9 of 17 patients with NHHPT [17]. Sestamibi was more successful, localizing a lesion in nine of nine patients, but the degree of overlap with the patients who had also undergone ultrasound was not reported [17]. An extensive analysis of the role of preoperative imaging in NHHPT found that, after controlling for multigland disease, the odds of Sestamibi localizing an adenoma were 0.53 compared with classic disease [16]. The odds of localization on ultrasound were similarly significantly low at 0.51. Furthermore, the two modalities were concordant in only 73.2% of cases of NHHPT vs. 87.1% for patients with a more typical biochemical presentation [16]. There is no robust data available regarding the utility of 4D CT in this diagnosis.

Intraoperative Findings and Decision-Making

Another challenge in the treatment of NHHPT is the higher observed incidence of multigland disease. Multigland involvement has been reported in 19–29% of patients with normal PTH levels, and up to 35% when both NHHPT and NCHPT are grouped together as mild variants of primary HPT [6, 9, 16, 17]. In contrast, in patients with classical disease, multigland hyperplasia was reported in 11–14% in the same series. One analysis did not support this finding, showing a comparable incidence of single adenomas in both the normohormonal and classic groups;

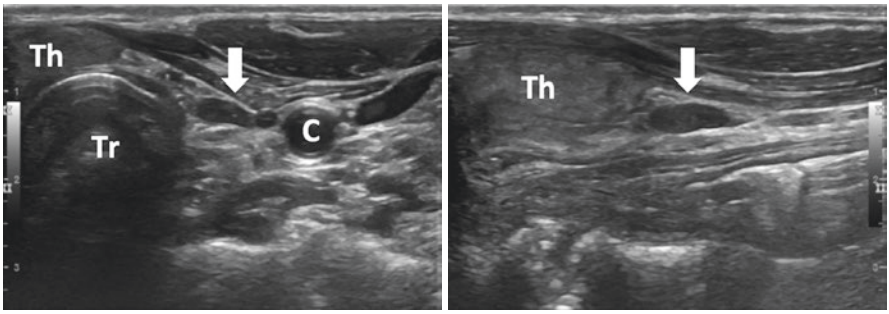

Fig. 8.1 Transverse (right) and sagittal (left) view on ultrasound show a hypoechoic lesion inferior to the thyroid lobe consistent with a parathyroid adenoma candidate (arrow). Th thyroid, Tr trachea, C carotid artery

however, the sample size of 11 was smaller than other studies [15]. Lower gland weight in NHHPT has also been reported by multiple groups, which is perhaps not unexpected, as PTH level has been shown to potentially correlate with glandular weight [14, 16, 22]. Figure 8.1 demonstrates a typically small-sized adenoma candidate in a patient with NHHPT, that was confirmed at the time of surgery.

Due to the short half-life of PTH, intraoperative PTH (IOPTH) has become a valuable tool in parathyroid surgery to ensure success and facilitate minimally invasive approaches. Traditionally, in patients with overt primary HPT and elevated serum PTH, a drop of ≥50% from the highest pre-incision or at excision level at 10 minutes, particularly when falling within normal reference range, strongly predicts surgical cure [23, 24]. Many have questioned the role of and expected change in IOPTH in the patient beginning with normal serum PTH values. Trinh et al. reported altered PTH degradation kinetics in NHHPT, observing a slower decay rate in NHHPT patients versus classic disease [15]. Consequently, the median time to biochemical cure as well as operative time was longer in this cohort. A ≥50% decrease in IOPTH correlated with operative cure in 97.8% of NHHPT patients, while cases in which IOPTH was not used exhibited a slightly lower cure rate of 95.1% [22]. The significantly delayed rate of IOPTH decay and longer operative time has been corroborated in other work [9]. In a series of 142 patients with mild HPT, 4.9% did not meet IOPTH criteria until after 20 minutes post excision, while 3.5% did not achieve an IOPTH drop of 50%. However, all patients on 6-month follow-up remained biochemically cured [8]. The sometimes dramatic IOPTH increase occurring after exposure and manipulation of the target gland but prior to excision is preserved in the majority of patients with NHHPT [6]. Furthermore, many patients with NHHPT have elevated baseline IOPTH levels, possibly attributable to anesthetic agents [25].

Overall, the literature maintains that the published goal of at least a 50% reduction in the highest baseline value should be achieved despite normal preoperative levels, as this decrement highly correlates with surgical success. Minimally invasive approaches therefore are still appropriate with localized

preoperative imaging in sporadic disease. However, given the greater likelihood of multigland disease in these patients, the surgeon should be prepared to perform a bilateral exploration if IOPTH has not shown the expected decrease. Longer operative times may also be planned to accommodate this circumstance as well as hormonal decay kinetics.

Long-Term Success and Outcomes

Following parathyroidectomy, disease persistence is generally diagnosed if biochemical markers are elevated within 6 months of the operation, while recurrence is suspected if hypercalcemia returns after at least 6 months of normocalcemia. One group reported an operative failure rate of 5% in mild disease (NCHPT and NHHPT) as compared with 1% for classic disease [7]. However, a large series of 1400 patients observed no difference in recurrence rates after surgery for mild versus classic HPT. Furthermore, of those who did recur, it was more common in the setting of NCHPT than NHHPT [9]. Several other studies also did not find significant differences in surgical success or complications for the two groups [6, 8, 14]. In patients cured with surgery, the mean postoperative PTH on long-term follow-up for NHHPT patients is also notably lower, with one group reporting an average level of 21 pg/mL compared with 43–58 pg/mL for classic disease, (dependent upon the degree of preoperative PTH elevation) [6]. There did not appear to be significant differences in postoperative serum calcium levels [6]. In patients with normal preoperative PTH values, following this value postoperatively has questionable utility, as cure is defined by normocalcemia.

To date, there is limited literature on the health and physiologic outcomes of patients with NHHPT. A study addressing the quality of life in mild primary HPT, in which 11 patients had NHHPT, showed significant improvements in all 10 categories of the SF-36 survey and equivalence with the general population in 9 categories following parathyroidectomy [26]. Operative management was again favored over observation in a randomized clinical trial by Talpos et al., who observed improvement in social and emotional functioning in the surgical group [27].

Recently, there has been significant focus on the cardiovascular effects of classic primary HPT, which is associated with hypertension, conduction abnormalities and arrhythmia, endothelial dysfunction, atherosclerosis, and metabolic syndrome, many of which improve after parathyroidectomy [28–31]. While there is insufficient data in NHHPT to make a conclusion regarding cardiovascular or metabolic benefit, initial studies are promising. Surgery has been shown to improve endothelial function and decrease carotid stiffness, particularly for patients with preexisting cardiovascular comorbidities [32].

Parathyroidectomy may also lead to normalization of lipid variables with subsequent decreased risk of cardiovascular death [33].

The benefit of parathyroidectomy on bone health in classic disease is well established. The only study specifically addressing bone mineral density changes in normohormonal disease suggests that the degree of improvement after parathyroidectomy may not be as robust as in overt primary HPT [34]. However, postoperative gains in bone density do seem to correspond with the degree of preoperative hypercalcemia [34].

Conclusions and Future Investigation

NHHPT is diagnosed with increasing frequency due to routine serologic testing of calcium levels. It is a biochemical diagnosis in which recognition of inappropriate or non-suppressed PTH secretion in the setting of hypercalcemia is paramount. Because these cases are typically detected incidentally, they are often considered asymptomatic and may not qualify for surgical management based on current NIH guidelines [19]. However, the physician must keep in mind that mild biochemical disease does not necessarily correlate with symptomatology. In contrast to NCHPT, the hypercalcemic state in NHHPT is more likely to contribute to symptomatic disease. Furthermore, the younger average age of patients in this cohort allows for a longer time in which end-organ complications of hypercalcemia develop [35]. The literature lacks robust prospective, longitudinal data reporting physiologic outcomes and serologic changes that compare surgery and medical management/observation specifically in patients with hypercalcemic, normohormonal disease. However, the available data summarized above suggests that parathyroidectomy may be both beneficial and highly successful in most cases.

The decision to operate on patients with NHHPT must be made carefully and only after exclusion of other causes of hypercalcemia. It is prudent to obtain multiple serum values of calcium and PTH preoperatively. This may solidify the diagnosis and will help rule out a spurious elevation. Because of the potential for multigland disease or smaller glandular mass, preoperative imaging may be non-localizing. A bilateral neck exploration may be required and should be performed by an experienced surgeon. The use of IOPTH is more critical when a focused approach is utilized, and the goal of reduction of ≥50% still applies despite normal preoperative values. Ultimately, however, while a decline in IOPTH may signify successful surgery, cure of NHHPT is defined by normalization of serum calcium levels, sustained for at least 6 months after surgery.

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Chapter 9
Subtle Variants of Hyperparathyroidism: Normocalcemic Hyperparathyroidism

Rohit Ranganath, Kendall F. Moseley, and Ralph P. Tufano

Introduction

Hypercalcemia is the hallmark of primary hyperparathyroidism (PHPT) and is due to hyperactivity of one or more parathyroid glands. Historically, PHPT typically presented with profound serum calcium elevations and associated altered mentation, renal failure, pathologic fractures, or Brown tumors of the bone. Today, these traditional clinical symptoms and signs of long-standing hyperparathyroidism are not frequently encountered due to improved assays and routine calcium and parathyroid hormone (PTH) testing [1, 2]. Patients with osteoporosis or nephrolithiasis may have their serum calcium and PTH levels checked as part of their diagnostic evaluation, leading to the diagnosis of PHPT. However, most patients with PHPT are now diagnosed after an incidental finding of an elevated serum calcium level. Although the guidelines for the management of asymptomatic PHPT have been well established, disorders of the parathyroid glands continue to challenge many clinicians [3].

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M. C. Singer, D. J. Terris (eds.), *Innovations in Modern Endocrine Surgery*,
https://doi.org/10.1007/978-3-030-73951-5_9

In addition to the classical variant of PHPT, in which both the calcium and PTH levels are elevated, two additional, subtle variants of PHPT are now recognized: normocalcemic and normohormonal (see Chap. 8). The normocalcemic variant of hyperparathyroidism will be the focus of this chapter.

The idea of normocalcemic hyperparathyroidism (NCHPT), characterized by universally normal calcium levels along with concurrent PTH level elevations, was first reported in the 1950s and 1960s [4, 5]. Subsequently, Siperstein and colleagues described this biochemical profile in a surgical cohort in the early 1990s. Silverberg and Bilezikian further characterized this as a distinct disease process in a small series of patients referred to specialty clinics for osteoporosis workup and management [6–8]. NCHPT was formally recognized as a distinct variant of PHPT during the proceedings of the National Institute of Health's Third International Workshop on Asymptomatic Hyperparathyroidism [3, 9].

Pathophysiology

The parathyroid glands work to ensure maintenance of calcium levels in a normal range via a negative feedback mechanism. Low circulating levels of serum calcium stimulate the release of PTH by the parathyroid glands. This is facilitated by the calcium-sensing receptor (CaSR) which is a G-protein-coupled receptor expressed by the parathyroid glands, gastrointestinal tract, and renal tubules. While, in the parathyroid glands, it facilitates PTH release, in the renal tubules, it has an inhibitory effect, reducing the reabsorption of calcium.

Three hypotheses to explain the pathophysiology of NCHPT have been proposed:

1. Rao et al. suggested that NCHPT is the first stage of a biphasic development of asymptomatic hypercalcemic hyperparathyroidism [10]. Patients in the first phase of this process typically have a period of normal to mildly elevated calcium levels with above normal PTH levels. With time, patients progress into the second phase and begin to display the overtly elevated calcium levels associated with the classical variant of PHPT.
2. A second hypothesis suggests that there is a diurnal fluctuation of calcium levels within a set range. For any individual, calcium levels may rise over that range which for them may represent a relative hypercalcemia but still may remain in the normal, population-based laboratory range [8, 11].
3. The development of renal and skeletal resistance to the effects of PTH is the basis for the third hypothesis for the development of NCHPT. In a study by Maruani and colleagues, when compared with patients with classical PHPT, patients with NCHPT did not show a decrease in PTH levels when challenged with a large oral calcium load [12].

Diagnostic Criteria

The diagnosis of NCHPT is made when PTH levels are persistently elevated (on at least two occasions) in the setting of both normal albumin-adjusted calcium and ionized calcium levels [13]. Crucially, prior to arriving at the diagnosis of NCHPT, all secondary causes for PTH elevation must be ruled out. Clinicians need to carefully assess patients for causes of secondary hyperparathyroidism. This is essential, as parathyroid surgery mistakenly performed in a patient with secondary disease rather than NCHPT may result in significant harm.

A common, though often overlooked cause of secondary hyperparathyroidism is insufficient calcium intake. As calcium feeds back on the parathyroid glands to suppress hormonal secretion, deficiencies in calcium intake, due to inadequate dietary (such as with dairy free diets) or supplemental consumption, will result in appropriate increases in PTH levels as the parathyroid glands act to mobilize calcium from skeletal stores. Current recommendations for calcium intake are 1000 mg daily for women less than 50 years old and men aged 70 or younger. For older individuals and those at risk of developing bone disease, the daily recommended calcium intake is 1200 mg [14, 15]. Prior to making a diagnosis of NCHPT, calcium consumption through diet or supplementation should be optimized to meet these goals.

Deficient or insufficient vitamin D levels are the most common cause of secondary hyperparathyroidism. Vitamin D, converted at the level of the kidney to its active form, or 1,25 dihydroxy vitamin D (calcitriol), is also important in suppressing PTH secretion. Additionally, calcitriol facilitates the absorption of calcium in the intestine. Thus, deficiency of vitamin D leads to PTH elevations through two different mechanisms – decreased direct negative feedback on the parathyroid glands and reduced intestinal uptake. Therefore, eliminating vitamin D deficiency as a possible cause of hyperparathyroidism before making the diagnosis of NCHPT is crucial. To this end, Cusano and colleagues recommend achieving a serum 25-hydroxy vitamin D level greater than 30 ng/ml, while the expert panel at the fourth NIH meeting recommended a level above 20 ng/ml [13, 16]. Importantly, in patients with vitamin D deficiency, PTH levels may lag for several months after repletion of vitamin D occurs. In some cases, optimization of both calcium and vitamin D in patients with previously normal serum calcium and elevated PTH levels may lead to frank hypercalcemia, ultimately "unmasking" the diagnosis of classical PHPT [17].

Kidney disorders may also lead to secondary hyperparathyroidism. Chronic kidney disease with a drop in GFR <60 cc/min can lead to elevated PTH levels. A GFR of at least 60 cc/min or greater rules out the possibility of renal-related secondary hyperparathyroidism [18, 19]. Idiopathic hypercalciuria, leading to a net loss of calcium, can cause secondary elevations of PTH, particularly with some variants of "renal leak" [20, 21]. Of note, there are conflicting data regarding the prevalence of PTH elevations in the setting of idiopathic or familial hypercalciuria, with some studies demonstrating that patients can present with normal PTH levels in the setting of hypercalciuria. While definitive conclusions linking hypercalciuria to

NCHPT cannot yet be reached, attempts to correct hypercalciuria (using potassium citrate or thiazide diuretics) should be made prior to diagnosing NCHPT [22–24].

Celiac disease and other gastrointestinal conditions that can cause calcium or vitamin D malabsorption can potentially result in secondary hyperparathyroidism [28]. Roux En-Y gastric bypass, a common procedure for weight loss, also frequently leads to hyperparathyroidism as a result of malabsorption. Secondary hyperparathyroidism is identified in as many as 35% of these patients within a year following surgery [29].

Drugs, like loop diuretics, lithium, anticonvulsants, and bisphosphonates, can lead to increases in PTH levels [25–28]. It is prudent to stop these medications if safe before making the diagnosis of NCHPT.

Epidemiology

True population-based studies which assess the prevalence of NCHPT are lacking. The studies examining this to date are from populations of patients referred for evaluation of metabolic bone disease or nephrolithiasis. This results in a significant selection bias. Published single institution experiences report the prevalence of NCHPT ranging from 0.4% to almost 9%. An international study with a small cohort reported a relative prevalence of NCHPT as high as 19% [24, 28]. A recent study of a cohort of individuals with hyperparathyroidism, who did not have a history of nephrolithiasis or metabolic bone disease, found a prevalence of 0.74% [30]. Among the largest cohorts in the United States reported to date is that of patients who were a part of the Dallas Heart study. In this group, the prevalence of NCHPT was 3% [31]. Another limitation of many of these studies is that they do not maintain strict adherence to criteria for diagnosis. For example, ionized calcium and vitamin D levels are sometimes not reported in some studies, and the process by which other secondary causes of hyperparathyroidism were ruled out were not described.

Clinical Features and Course of Disease

In many patients, the diagnosis of NCHPT is made after the patient has presented with osteoporosis, a fragility fracture, or nephrolithiasis. As in the case of classical PHPT, it can be assumed that the screening, rather than symptoms, revealed the disease. Some authors have categorized NCHPT patients into two variants [7]. In one variant, there is evidence of end-organ damage (skeleton, kidney), but the patient is asymptomatic; in the second variant, or the precursor stage, the patient has neither symptoms nor evidence of end-organ damage [32].

Osteoporosis (57%), with or without fragility fracture (11%), and nephrolithiasis (14%) are the primary clinical features of NCHPT [8]. Hypertension and metabolic

disturbances, such as hyperlipidemia, insulin resistance, and glucose intolerance, are seen in these patients as well [33].

In classical PHPT, metabolic bone changes (osteoporosis), measured by diminished bone mineral density (BMD) on dual-energy X-ray absorptiometry (DXA), are most prominent at the distal one-third of the radius [8, 34]. In contrast, in NCHPT, osteoporosis is more common in the lumbar spine (34%) and hip (38%) compared with the radius (28%). At least one of these sites is involved in 8% of NCHPT patients.

Nephrolithiasis is also present in a significant number of patients with NCHPT [37]. A recent study has postulated that polymorphism in the CaSR gene may be the reason for nephrolithiasis despite serum calcium levels being normal [38]. A study also demonstrated that, when cinacalcet is used in combination with a calcium-controlled diet, there was a reduction in both the size and number of renal stones in both patients with classical and normocalcemic variants of HPT [39].

PHPT is known to increase arterial stiffness, leading to hypertension and an increased the risk of cardiovascular events [40]. Tordjman and colleagues demonstrated that arterial rigidity and cardiovascular risk factors in NCPHT are similar to classical PHPT, although the morbidity may be lower in the normocalcemic variant [41]. In another study, a small cohort of 11 patients with NCHPT demonstrated significantly higher systolic and diastolic blood pressures compared with subjects with normal PTH levels [42].

Metabolic abnormalities, such as hyperlipidemia, insulin resistance, and glucose intolerance, are known issues in PHPT. Data has emerged from small cohorts that patients with NCPHT appear to experience similar metabolic dysfunction. Impaired glucose tolerance is a significant feature of NCHPT compared with normal controls. However, no significant impact on HbA1c levels or insulin sensitivity has been found.

Dyslipidemia is a risk factor for cardiovascular events. Low-density lipid levels have been found to be significantly elevated in patients with NCHPT compared with patients with hypercalcemic PHPT in two recent studies [43, 44].

Nonspecific Symptoms

More than 50% of patients labeled as asymptomatic in classical PHPT report nonspecific symptoms such as fatigue, bone/joint pain, memory and concentration problems, irritability, depression, anxiety, sleep problems, and increased thirst [45]. Interestingly, as symptoms do not appear to correlate with increased blood calcium levels, their presence has been excluded as a criteria for surgery in patients with PHPT [46]. Though many series report overall patient improvement in neurocognitive parameters after surgery, the data is mixed as to whether symptoms and quality of life scores improve after successful surgery [47–50]. A prospective, multicenter study from France showed that patients with NCHPT have similar nonspecific symptoms diminishing their quality of life. The quality of life score based on responses to the SF-36 questionnaire did show a significant improvement after

surgery in the NCHPT cohort [51]. Although these nonspecific symptoms improved in patients with NCHPT after surgery, they resolved to a lesser extent than in the hypercalcemic group.

Natural History of NCHPT

In one of the largest cohorts of patients with NCHPT, approximately 19% of patients became hypercalcemic over a 6-year follow-up period, while the majority remained eucalcemic [52]. In a NCHPT cohort described by Tordjman and colleagues, of the 32 patients in the cohort, only 12 underwent parathyroid surgery. Of the 20 patients who were managed medically, none progressed to hypercalcemia over a 4-year follow-up [35]. No clear data is yet available on which patient or disease factors put patients at most risk of developing frank hypercalcemia. In one study, older age and higher baseline serum and urinary calcium levels were associated with progression [8].

Management of NCHPT

Unlike classical variant of PHPT, there are no current guidelines for the optimal management of NCHPT. This is largely due to a relative lack of research and a precise understanding of the clinical ramifications of NCHPT.

In general, it is reasonable to consider surgery in those patients who have manifestations of end-organ damage (such as osteoporosis or nephrolithiasis) in whom all secondary causes of hyperparathyroidism have been definitively ruled out. However, when patients do not have any symptoms or have not developed complications due to the disease, close monitoring with annual clinical assessment, biochemical testing, and imaging, when appropriate, is reasonable. Medical management, with alendronate and vitamin D, has been evaluated in a small clinical trial of 37 postmenopausal women with osteoporosis and NCHPT. In this group, BMD improved in the lumbar spine and hip, while the women treated with vitamin D only exhibited progressive bone loss [53].

Surgical Management of NCHPT

With improvements in imaging to localize pathologic parathyroid glands, minimally invasive or focused, parathyroidectomy has gained widespread acceptance in the management of PHPT. It provides the benefits of avoiding unnecessary

neck exploration, obviating the risk of bilateral recurrent laryngeal nerve injury and preventing the potential devascularization of normal glands. Preoperative localization and intraoperative PTH testing are the foundation of focused parathyroidectomy.

Ultrasound, sestamibi single-photon emission computerized tomography (SPECT-CT), and four-dimensional CT scan are the most commonly used parathyroid localization modalities. Ultrasound of the neck has a high specificity (over 90%), but the sensitivity varies widely with operator experience [54]. Sestamibi SPECT-CT has a sensitivity of over 70% with a high positive predictive value [55]. Multiphase CT scans have a sensitivity of over 80% and provides anatomical detail. These CT scans have the advantage of more accurately detecting multiglandular disease. This ability is particularly beneficial in NCHPT, in which multigland disease is quite common [56–58]. While there is concern about the radiation exposure with the multiphase scans, a single-institution study has demonstrated that a standardized, two-phase CT, read by an experienced radiologist, may be adequate in localizing diseased glands [59]. When any two imaging modalities are concordant, the positive predictive value is as high as 99% [60].

While more than 80% of cases of PHPT is due to a single adenoma, surgical cohorts have shown that, in NCHPT, multigland disease is significantly more common. Studies have reported a prevalence of multiglandular disease ranging from 13% to 53% in this population [36, 52, 61–64]. The pathologic gland or glands in NCHPT are also frequently smaller than those seen in hypercalcemic PHPT [62]. Hence, the sensitivity of scintigraphy is significantly lower in normocalcemic disease [52, 65]. Due to these factors, preoperative localization may therefore be less successful in NCHPT, and four-gland exploration may be necessary more often than it is typically employed for patients with classical PHPT.

Intraoperative PTH testing (IOPTH) is an accurate intraoperative adjunct that, when used in focused parathyroidectomy, ensures a 97–99% chance of cure in hypercalcemic PHPT [66, 67]. A IOPTH drop of 50% or more from baseline, at 10 min post excision, and into the normal range (dual criteria) ensures biochemical cure [65]. Trinh and colleagues studied the utility of IOPTH in 119 patients with NCHPT and 497 patients with classical hyperparathyroidism. Patients with classical hyperparathyroidism demonstrated higher baseline PTH values. IOPTH decay kinetics were found to be similar and could be utilized accurately to assess cure in both groups. A higher rate of conversion to bilateral exploration was observed in the NCHPT group.

A recent multi-institutional study with over 700 patients confirmed that the prevalence of multigland disease is higher in NCHPT. When compared with patients with classical PHPT, those with NCHPT required subtotal parathyroidectomy more frequently and had a higher rate of remedial surgeries [68, 69].

Outcomes After Parathyroidectomy

In one of the first reports on outcomes after parathyroidectomy, Koumakis and colleagues reported that, 1 year after surgery, patients with NCHPT and osteoporosis showed a significant increase in BMD in the spine and hip [70]. Traini and colleagues reported that, in patients who had preoperative evidence of nephrolithiasis, surgery achieved biochemical cure, and 40% showed no new evidence of nephrolithiasis. In 60% of the patients, microliths persisted, but the patients did not have any symptoms. BMD improved in 41% of the patients, while, in 50%, the bone disease was stable [61].

In a recent surgical cohort of 71 patients with NCHPT, 6 months after parathyroidectomy, 53% of patients had normal PTH levels, while 46% had elevated PTH levels. There was no difference between the two groups in terms of single vs multigland disease, surgical approach, or rates of subtotal parathyroidectomy. On multivariate analysis, the predictors of elevated postoperative PTH levels were as follows: preoperative PTH levels > 100 pg/ml and PTH level at 30 min > 30 pg/ml. They found that BMD improved 5.6% in patients who had normalization of PTH levels, while no significant change was seen in BMD in patients who failed to normalize [63].

After surgery, for NCHPT patients, there is neither a clear definition of long-term cure nor clear recommendations for follow-up. As these patients are normocalcemic, PTH levels alone can be used to determine outcomes. The American Association of Endocrine Surgeons guidelines define surgical cure in NCHPT as when PTH levels normalize at 6 months [71]. When that fails to materialize, they recommend reevaluating the patient for secondary causes and carefully following the patient for recurrence.

Conclusion

NCHPT is increasingly recognized as a distinct variant of hyperparathyroidism. Osteoporosis and nephrolithiasis appear to be the predominant features that draw attention to these patients. Secondary causes of hyperparathyroidism should be diligently ruled out prior to making the diagnosis. While surgery for select patients does appear to provide benefits, the precise criteria for surgical intervention are yet to be determined (Fig. 9.1).

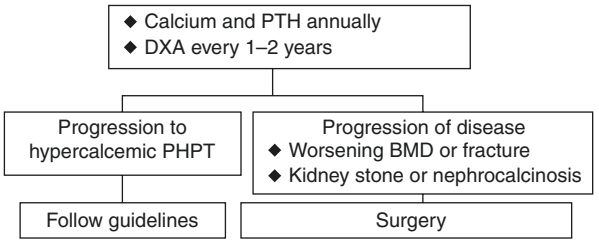

Fig. 9.1 Algorithm for management of NCHPT

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Chapter 10
Indications for Parathyroidectomy

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The parathyroid glands were first discovered in 1850 by Sir Richard Owen, the curator of the Natural History Museum of London. He described a "small compact yellow glandular body attached to the thyroid at the point where the veins emerge" following the autopsy of a rhinoceros [1]. German pathologist Rudolph Virchow may have identified the parathyroid gland in 1863 when describing the cervical region, but it was not until 1880 that Ivar Sandström, a medical student at the time, definitively demonstrated the existence of parathyroid glands in a human through meticulous cadaveric dissection and documentation [1, 2].

Felix Mandl, a Viennese surgeon, was the first to demonstrate the relationship of the parathyroid glands and their removal with calcium homeostasis and bone health. He also demonstrated successful control of hypercalcemia with resection of a parathyroid adenoma in 1925. Mandl, along with David Barr and Harold Bulger, helped develop and define the clinical presentation of hyperparathyroidism in the late 1920s.

Parathyroid-Related Hypercalcemia

Typically, there are four parathyroid glands, two superior and two inferior, each weighing 30–50 milligrams [3–5]. Accessory or supernumerary parathyroid glands are found in approximately 13% of individuals at autopsy [3, 4]. Ectopic parathyroid tissue occurs in 15%–20% of humans [5]. Ectopic parathyroid glands can be

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M. C. Singer, D. J. Terris (eds.), *Innovations in Modern Endocrine Surgery*,
https://doi.org/10.1007/978-3-030-73951-5_10

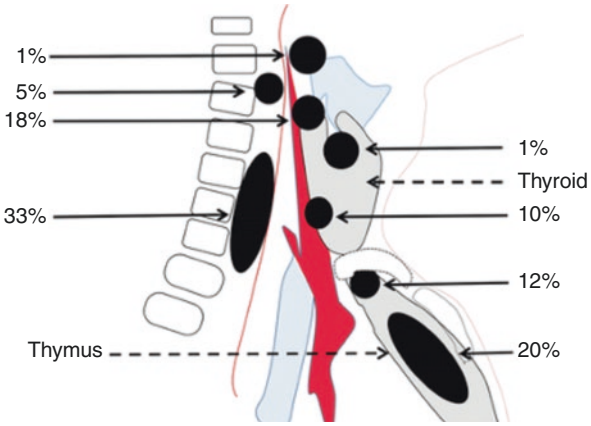

Fig. 10.1 Sagittal view of the neck depicting locations of ectopic parathyroid tissue. The carotid artery, thyroid cartilage, cervical vertebrae, and sternum are depicted as well. Frequency of ectopic location is depicted with percentages that ectopic tissue is found in noted location

located anywhere along the tract of thymic descent [1–5]. Figure 10.1 depicts common ectopic parathyroid tissue locations and their relative frequencies [6].

The parathyroid glands develop during the fifth and sixth weeks of gestation. The inferior parathyroid glands arise from the third pharyngeal pouch, and the superior parathyroid glands arise from the fourth pharyngeal pouch [6–10]. The inferior parathyroid glands migrate with the thymus caudally and medially. This accounts for the more variable location of these glands.

Parathyroid hormone helps regulate the body's calcium homeostasis by affecting bone mineral turnover, renal calcium reabsorption, and dietary enteral calcium absorption. As calcium measurements have become part of routine blood work, there is an emerging trend of earlier disease presentation and an increased incidence of normocalcemic primary hyperparathyroidism. Some studies demonstrate clinical benefit to surgical management in this population, given its cost-effectiveness, versus continued chemical monitoring and the value of prevention of end-organ damage [9, 10]. Stephen et al. found that surgical management in asymptomatic individuals with normocalcemia hyperparathyroidism was associated with decreased rates of renal dysfunction, osteoporosis, and cardiovascular disease later in life [4].

The most common cause of primary hyperparathyroidism, accounting for 85% of cases, is a single parathyroid adenoma [5, 11]. In some cases, there is a second adenoma that is also hypercellular and producing excessive parathyroid hormone but has been suppressed by the first adenoma. Multiple synchronous parathyroid adenomas have been reported in up to 10% of individuals [1, 11]. Four-gland hyperplasia accounts for approximately 15% of primary hyperparathyroidism cases, followed by parathyroid carcinoma in <1% of primary hyperparathyroidism cases [7].

Parathyroid carcinoma may present as a hypercalcemic crisis. The cause of parathyroid carcinoma is unknown, but it is associated with several syndromes and known genetic mutations. HRPT2/CDC73 is a tumor suppressor gene located on chromosome 1 and encodes parafibromin, a protein that is involved in regulation of gene expression and inhibition of cell proliferation [12, 13]. Mutations in this gene have been linked to both familial and sporadic cases of parathyroid carcinoma.

Mutations in PI3K, AKT, and MTOR pathways have also been demonstrated with whole-exome sequencing. Parathyroid carcinoma is associated with higher serum levels of parathyroid hormone, often five to ten times higher than levels associated with single or multiple adenomas. It is also associated with significantly higher serum calcium levels (greater than 14 mg/dL) [12, 13].

Effects of PTH-Mediated Hypercalcemia

Parathyroid hormone is crucial to vitamin D homeostasis. Normal vitamin D absorption and activation start with dietary intake of D_2 or D_3 or 7-dehydrocholesterol activation with 290–315 nm ultraviolet B radiation (sunlight exposure to the skin) [14]. The liver then hydroxylates it to form 25-hydroxyD. Parathyroid hormone, released in response to low serum calcium levels, causes renal hydroxylation of 25-hydroxyD to $1,25(OH)_2D$, the bioactive form [14]. Secretion of parathyroid hormone signals increased renal absorption of calcium, increased renal excretion of phosphate, and increased synthesis of $1,25(OH)_2D$, which increases intestinal absorption of calcium and binds to osteoblasts, activating a signaling cascade which prevents bone growth [14, 15]. With normal parathyroid glands, this physiology promotes appropriate calcium homeostasis. In primary hyperparathyroidism, this pathophysiology leads to elevated serum calcium levels. Hypercalcemia is important to address due to its ability to cause end-organ damage when levels remain elevated over time. Assadipour et al. reported that 62% of patients demonstrated evidence of at least one type of end-organ damage related to hypercalcemia within 5 years of a primary hyperparathyroidism diagnosis [11].

Hypercalcemia can negatively impact renal function through direct injury resulting from nephrocalcinosis and hypercalciuria. It can also lead to chronic renal insufficiency indirectly secondary to nephrolithiasis. Renal function is often calculated and reported as the estimated glomerular filtration rate (eGFR), and primary hyperparathyroidism is associated with decreased eGFR even in the absence of nephrolithiasis or nephrocalcinosis. However, rates of renal dysfunction in patients with primary hyperparathyroidism are decreasing due to the trend toward early diagnosis of primary hyperparathyroidism.

Bone health is also impacted by primary hyperparathyroidism. As noted above, parathyroid hormone binds to osteoblasts and stimulates a signaling cascade that results in bone resorption. In the absence of new bone formation, bone loss becomes permanent, and osteopenia followed by eventual osteoporosis ensues [15, 16].

Hypercalcemia as a result of primary hyperparathyroidism can also have a detrimental effect on the cardiovascular system. Several studies have demonstrated increased rates of atherosclerosis, hypertension, left ventricular hypertrophy, heart failure, arrhythmia, and valvular calcific disease [17, 18]. The mechanism behind at least some of this dysfunction is thought to be due to excess parathyroid hormone action on G-protein-coupled receptors in the heart resulting in changes to myocyte contractility, hypertrophy, and proliferation (this also likely leads to endothelial

changes in the vasculature) [18]. Valvular disease can also develop from the direct effect of calcium deposition [17].

When to Intervene

Hypercalcemia can be managed medically, but the definitive treatment for primary hyperparathyroidism is surgery. Medical management is limited to patients who are not surgical candidates or choose not to have surgery. Cinacalcet is the only medication that has been demonstrated to decrease serum calcium levels without changing serum parathyroid hormone levels demonstrably and with no effect on bone mineral density. [9] Bisphosphonate therapy has been demonstrated to improve bone mineral density, and alendronate, specifically, has been shown to improve density in the lumbar spine for patients with nonsurgically managed primary hyperparathyroidism without affecting serum calcium levels [9]. In the setting of critically high hypercalcemia, aggressive intravenous hydration with diuresis or even dialysis can palliate the situation until appropriate medication can be given or surgery can be performed.

Indications for Surgery

Historically, patients were identified with primary hyperparathyroidism only at the point that they demonstrated clear sequelae of the disease, such as pathologic fractures or recurrent nephrolithiasis. However, with patients now typically being identified earlier in their disease course, the value and need for surgery have become a more relevant clinical question. There is widespread agreement that "symptomatic" patients, often defined as experiencing a pathologic fracture or nephrolithiasis, should undergo surgery. The benefit of surgery in these patients is felt to be manifest.

Greater debate exists over the value of surgery in so-called "asymptomatic" patients. The National Institutes of Health (NIH) has published a series of consensus guidelines addressing this cohort. In the most recent version, published in 2014, surgery was recommended for asymptomatic patients who were younger than 50 years old, had a serum calcium of 1 mg/dL or more above the upper limit of normal, demonstrated a bone mineral density T-score on DEXA less than or equal to −2.5, had a creatinine clearance less than 60 milliliters per minute or a 24-hour urine calcium greater than 400 mg/d, or had nephrolithiasis or nephrocalcinosis identified on radiology imaging [19]. Recently, the American Association of Endocrine Surgeons (AAES) published their consensus guidelines on parathyroidectomy [20]. Those recommendations largely mirror the NIH suggestions.

However, the question of who should be considered "asymptomatic" remains an open debate. Data continues to accumulate which demonstrate that "asymptomatic" patients are often not truly asymptomatic and that many patients benefit from surgery regardless of symptoms. Many additional symptoms, such as neurocognitive

impairment and sleep disturbances, are in at least some patients attributable to their primary hyperparathyroidism. Consequently, the AAES guidelines extend their recommendations beyond those of the NIH. For patients that exhibit neurocognitive or neuropsychiatric symptoms attributable to hyperparathyroidism, surgery is recommended. Additionally, other possible manifestations of the disease, including muscle weakness, abnormal sleep patterns, and gastroesophageal reflux, can be considered when weighing the value of possible surgery. Debate about the optimal indications for surgery will continue until more definitive evidence regarding the benefits of surgery is gathered.

In the setting of reoperative surgery, in which the risk of failure and complications is greater, the threshold to proceed with surgery should be greater than in primary surgery. The American Head and Neck Society and British Association of Endocrine and Thyroid Surgeons (AHNS/BAETS) recently published guidelines on reoperative management of parathyroid disease [21] and recommend that surgeons carefully reassess the indications and potential benefits of surgery in the context of the greater complexity of reoperative cases.

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Part III
Surgical Adjuncts

Chapter 11
Intermittent Neuromonitoring of the Recurrent Laryngeal Nerve

Erin P. Buczek, Dipti Kamani, and Gregory W. Randolph

Introduction

Thyroid and parathyroid surgery has evolved into an elegant modern-day operation with a focus on surgical and voice outcomes. Recurrent laryngeal nerve (RLN) injury is one of the most dreaded complications in endocrine surgery. Unilateral RLN injury causes significant morbidity to the patient and not only impacts voice but can also lead to aspiration and dysphagia. Bilateral RLN injury often results in severe airway compromise and tracheostomy.

Factors that can impact risk of RLN injury include surgeon experience and volume, malignancy, revision surgery, and patient-specific considerations such as anatomical variants. The rate of permanent nerve injury ranges from 0.5 to 5%, whereas transient nerve paralysis ranges from 1 to 30%, depending on surgeon experience and volume [1]. Notably, reported rates of RLN paralysis are likely underestimated due to difficulty in recognition of intraoperative injuries as well as inconsistency in performing postoperative laryngeal examination and reporting of injuries.

In 1938, Lahey described routine dissection and identification of the RLN during thyroid surgery [2]. Since then, direct visualization of the RLN has been the gold standard for preventing nerve injury [3]. Prior to the introduction of RLN intraoperative nerve monitoring (IONM), surgeons relied on the visual appearance of the

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M. C. Singer, D. J. Terris (eds.), *Innovations in Modern Endocrine Surgery*,
https://doi.org/10.1007/978-3-030-73951-5_11

nerve to determine its probable postoperative functional status. While visualization is certainly critical for preservation of function, it is evident that a visually intact RLN does not always correlate with a functionally intact nerve [4]. Compression, thermal, and traction injuries can result in severe dysfunction or permanent paralysis, yet the nerve may appear visually intact. Unfortunately, visual inspection alone is not reliable, and one study even concluded that 90% of nerve injuries in thyroidectomies cannot be diagnosed visually [5].

IONM provides an invaluable tool for assessing the functional status of the nerve. IONM delivers real-time information regarding the status of the RLN and can help guide intraoperative decision-making. Recognition of unilateral injury and the decision to proceed with contralateral surgery is perhaps one of the greatest benefits of IONM.

Background

Challenges in IONM Adoption

Since the introduction of IONM, there have been several barriers to its adoption into widespread use, principally the perception of its higher cost and questions regarding improved outcomes. In the past, greater cost, including both equipment and operative time costs, has been cited as an argument against the use of IONM. In a recent study by Al-Quaryshi et al. using rates of contralateral RLN palsy ranging from 1 to 17%, IONM incorporation into intraoperative decision was actually the most cost-effective algorithm [5].

Another challenge is establishing benefits of IONM due to difficulty in demonstrating a statistically significant decrease in RLN paralysis. One recent study that evaluated the challenges in reporting the role of IONM recognized the nonuniformity across institutions regarding preoperative laryngoscope, intraoperative utilization of monitoring, and postoperative laryngoscopy as an important issue [6]. Additionally, most studies do not identify and consider other confounding factors that impact the results, including surgeon's expertise and familiarity with IONM, use of audio-based systems, underlying disease, and the extent of surgery. Dralle et al. evaluated the projected required enrollment in a study to truly assess a difference in outcomes with and without IONM and determined that an adequately powered study of RLN outcomes would require 9 million patients per arm in benign disease and 40,000 per arm in malignant disease [7]. Higgins et al., Lombardi et al., and Pisanu et al. have conducted separate meta-analyses, all of which found no difference overall with or without nerve monitoring [8]. However, they cautioned researchers to use discretion, as most of the studies were non-randomized observational studies. The Scandinavian Endocrine Surgical Quality Registry showed lower rates of permanent RLN paralysis with neural monitoring [9]. A retrospective study by Barczynski et al. reported on 850 patients with revision surgeries and demonstrated a statistically significant decrease in the rate of transient RLN paralysis [10].

IONM Application in Present-Day Clinical Practice

IONM is now utilized by a large group of both head and neck and general surgeons. The American Head and Neck Society recommends use of IONM during high-risk surgery, in revision thyroid surgery, and in cases with preoperative vocal cord paralysis [11]. The 2015 American Thyroid Association guidelines and the ATA Surgical Affairs Committee both discuss the utilization of IONM and its use in determining functionality of the nerve [12–14]. When exposed to IONM during their training, over 95% of endocrine fellows continue to use IONM in some or all of their cases in practice [15]. Surveys of both recently fellowship trained endocrine and head and neck surgeons reported that 60% of these surgeons always use IONM, 36% use it selectively, and only 5% never use it [15]. Utilization has substantially increased in the past several years with approximately 80% of head and neck surgeons and 65% of general surgeons in the USA utilizing IONM [16, 17].

Application of Intraoperative Nerve Monitoring

According to the International Standards Guidelines Statement developed by the International Neuromonitoring Study Group (INMSG), IONM has three basic applications [18].

1. *Identification/neural mapping of the RLN*: The nerve is mapped out initially through stimulation and then is also visually identified. Several studies have shown that use of IONM improves speed of identification and is associated with nerve identification 98–100% of the time [19, 20]. Stimulation of neural and nonneural structures can help in tracing the nerve and its branches. IONM is particularly useful in revision surgeries, as scar tissue makes nerve identification difficult, as well as in surgeries involving large goiters and invasive malignancies, when normal anatomy is altered.
2. *Insight into pathologic states of the RLN:* IONM is valuable in demonstrating residual electrical activity in the setting of less than normal, preexisting nerve function. For example, a nerve invaded by malignancy can retain significant residual electromyography (EMG) response, which can be revealed by active stimulation with IONM. Even when the vocal cord is paralyzed, residual EMG activity can still be present. In a recent study by our group, we found that about a third of the patients with VCP resulting from malignant invasion of the nerve demonstrated significant EMG activity [21]. Thus, IONM can provide important insights in the functioning of invaded nerves, which is not obtainable otherwise. The surgeon needs to be cognizant about the postoperative outcome of the excision of a nerve with residual EMG on IONM in a setting of VCP, as resultant functional issues such as dysphagia and aspiration may occur. A recently published INMSG guideline emphasizes this point and delineates management of an invaded RLN based on preoperative laryngeal exam and intraoperative IONM EMG data [22].

3. *Prognostication of postoperative neural function and lesion site identification*: IONM provides improved accuracy of prognostic testing, specifically directed at prevention of bilateral RLN injury. Bergenfelz et al. evaluated over 3600 endocrine cases and reported that only 11.3% of injuries were predicted by surgeons, and furthermore, only 16% of bilateral injuries were recognized intraoperatively [23]. Conversely, IONM is far more precise, with several studies showing a 92–100% negative predictive value, with normal EMG activity associated with normal postoperative neural function [24–28].

Negative Predictive Value (NPV)

The NPV refers to the probability that patients with maintenance of a normal EMG signal at the completion of surgery will have normal postoperative vocal cord function. Successful EMG with stimulation of the ipsilateral vagus nerve is associated with a high negative predictive value in multiple series (92–100%) [7, 26, 27, 29–34]. IONM can be used to consistently and accurately predict normal neural function with successful EMG stimulation at the conclusion of the case.

Positive Predictive Value (PPV)

For IONM, PPV refers to the probability that LOS at the completion of surgery will predict vocal cord dysfunction postoperatively [32]. Dralle et al. reviewed several studies with an average PPV of 45% but with a large range from 10% to 90% [24–28, 35, 36]. PPV is more variable than NPV due to differences in troubleshooting algorithms and the lack of uniform definitions of LOS amplitude among providers (i.e., using a lower amplitude to define LOS results in a higher PPV) [29].

Technique

Equipment

A variety of neural monitoring methods have been described including glottic observation, laryngeal palpation, endotracheal tube (ETT)-based surface electrodes, and post-cricoid surface electrodes [11, 18, 37]. The most preferred IONM method is using an ETT-based system that includes both audio and visual feedback, using graphic documentation of the EMG waveform from the thyroarytenoid muscle (Fig. 11.1). This method is superior to an audio-only method as it allows for visualization of the amplitude, latency, and morphology of the EMG waveform. Either a

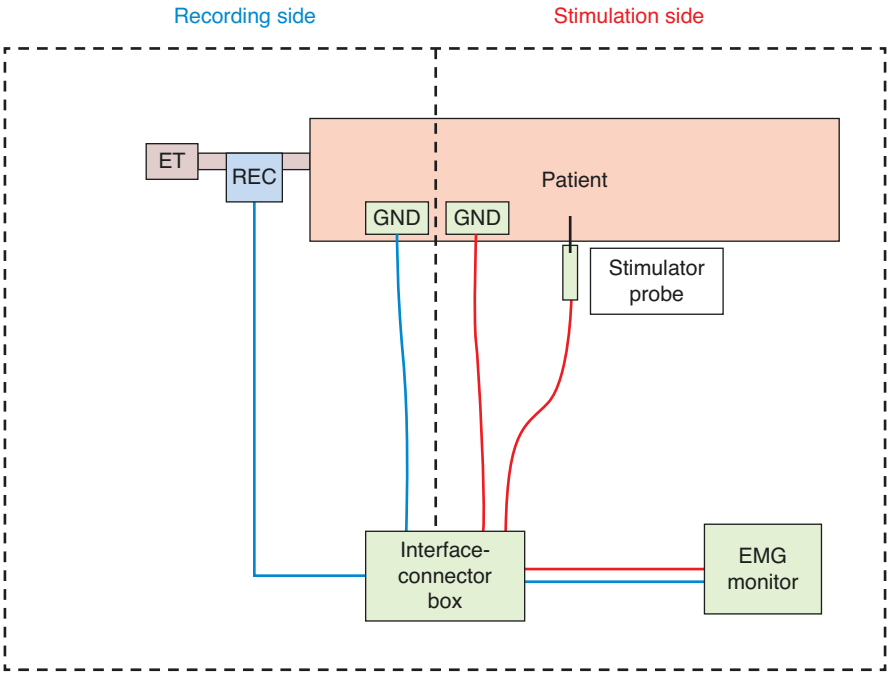

Fig. 11.1 Standard IONM equipment setup using endotracheal tube surface electrodes. ET endotracheal tube, GND ground electrodes, REC recording side, EMG electromyography. (Copyright © Gregory W. Randolph [42])

pre-manufactured ETT with electrodes or a standard ETT with thin adhesive electrodes placed over the tube can be utilized. Electrocautery units should be kept at least 10 feet away from the neural monitoring unit to avoid electrical interference. Ground electrodes can be placed on the shoulder or sternum.

Anesthesia Considerations

Preoperative communication between the surgeon and anesthesia team is imperative for the success with IONM. Muscle relaxants may interfere with the EMG response and use of prolonged muscle relaxants should be avoided. The endotracheal tube should be placed without the use of lubricants and positioned with the electrodes touching both vocal cords (Fig. 11.2). The International Guidelines support the use of a drying agent such as glycopyrrolate and suction, which may help improve contact between the vocal cords and electrodes [18]. As some anesthesia providers twist the ETT as it passes through the glottis during intubation, it is important to confirm that the electrodes are oriented properly against the vocal cords. Recently, based on their own experience with over 3000 nerves, Macias et al. have published an

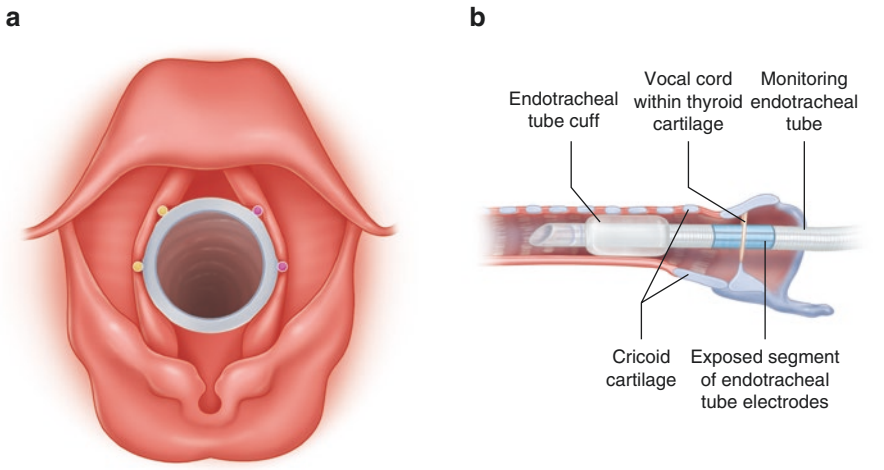

Fig. 11.2 Proper placement of the endotracheal tube. The exposed surface (represented by black lines) of the ETT electrodes is abutting the luminal aspect of the vocal cords. Care should be taken to avoid rotation of the electrodes. (**a**) Endoscopic view. (**b**) Lateral view. (Copyright © Gregory W. Randolph [42])

up-to-date nerve monitoring protocol particularly focused on anesthesia parameters that are essential for successful IONM [38].

Prior to securing the tube, the patient should be carefully positioned for surgery, including neck extension, which can cause up to 6 cm of movement of the ETT [39]. After the neck has been extended, the electrode positioning should be verified. This can be done with direct visualization or by the presence of respiratory variations on the EMG (Fig. 11.3). Respiratory variations are small waveforms with amplitudes in the range of 30–70 μV that cause coarsening of the EMG. These can be visualized when the anesthetic is "light," right before a patient spontaneously moves, coughs, or "bucks" [40].

An additional check to ensure satisfactory placement is to evaluate the impedance as a higher impedance imbalance may indicate inappropriate tube placement. A high overall impedance requires that the ground electrodes be checked. The overall impedance should be less than 5 Ω and the imbalance between the two sides should be less than 1 Ω.

IONM Data Gathering

One of the challenges of comparing IONM outcomes with traditional visualization methods is the lack of consistent data gathering. Standard data that should be documented includes a preoperative laryngeal exam (L1), initial intraoperative suprathreshold vagal nerve stimulation (V1), initial intraoperative RLN stimulation (R1),

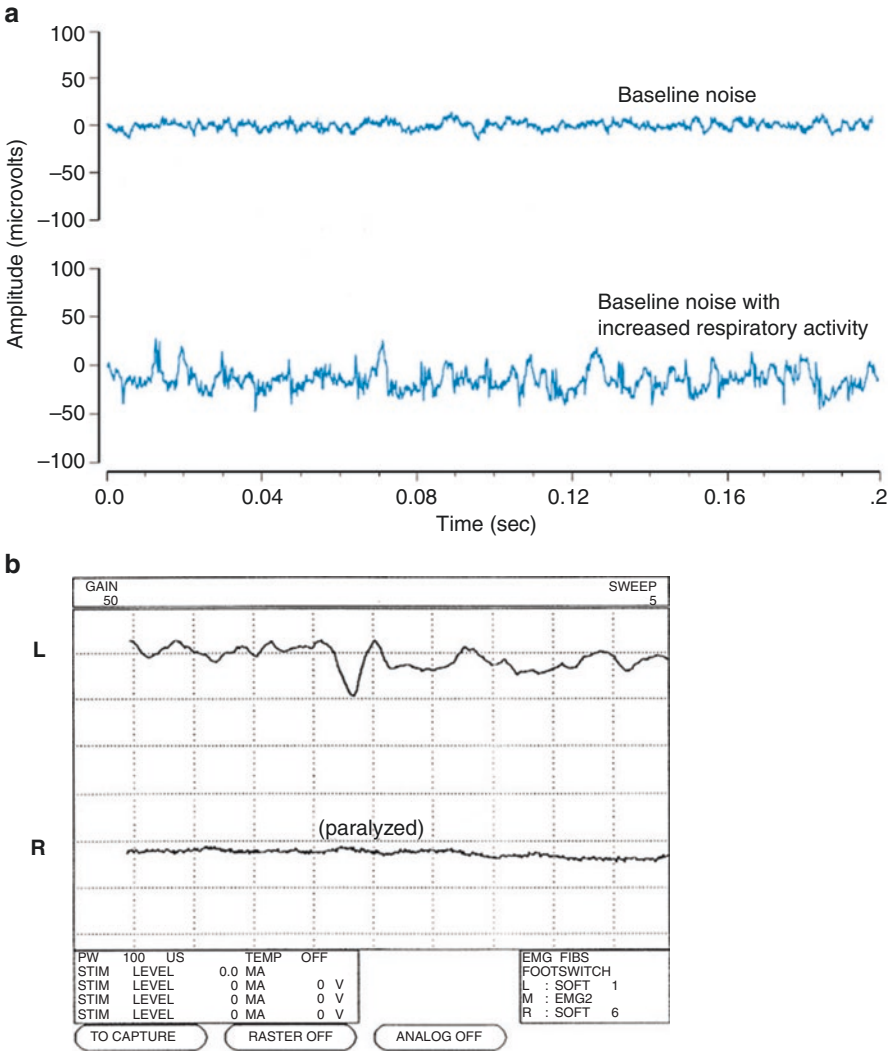

Fig. 11.3 (**a**) Respiratory variation and baseline tracings in a patient. (**b**) The left vocal cord shows normal respiratory variation between 30 and 70 μV, while the right vocal cord is electrically silent due to paralysis. (Copyright © Gregory W. Randolph [42])

post-dissection intraoperative RLN stimulation (R2) and post-dissection vagal stimulation (V2), as well as a postoperative laryngeal exam (L2) [41, 42]. Neural mapping and vagal stimulation can be performed at a suprathreshold current of 2 mA; when the nerve has been visualized, the current can be reduced to 1 mA for further testing and prognostication. The monitor event threshold should be set at 100 μV and the stimulator probe to a pulsatile output of 4 per second.

Electromyography (EMG) Waveform: Amplitude, Latency, and Threshold

The monitoring waveform is an important component of accurate intraoperative interpretation of EMG data. The amplitude is defined as the vertical height of the apex of the positive initial waveform deflection to the lowest point in the subsequent opposite polarity phase of the waveform (Fig. 11.4). The INMSG defined latency as the time from the stimulation spike to the appearance of the first evoked waveform peak. Latency recordings are useful not only to differentiate nonneural structures from neural structures but also to distinguish RLN, the superior laryngeal nerve, and the vagus nerve. Normative EMG and waveforms have been described and are depicted in Fig. 11.5 [43]. Changes in latency during a case can also indicate occult neural injury and should be closely evaluated.

Loss of Signal

Establishing an Adequate Baseline

According to the latest guidelines from the INMSG, an initial amplitude of 500 μV or greater is an attainable goal with a stimulation of 1–2 mA [32]. This has served as an initial baseline in several studies [44–47]. Waveform morphology anomalies which can confound an accurate EMG are more likely to occur if the amplitude is <350 μV [45].

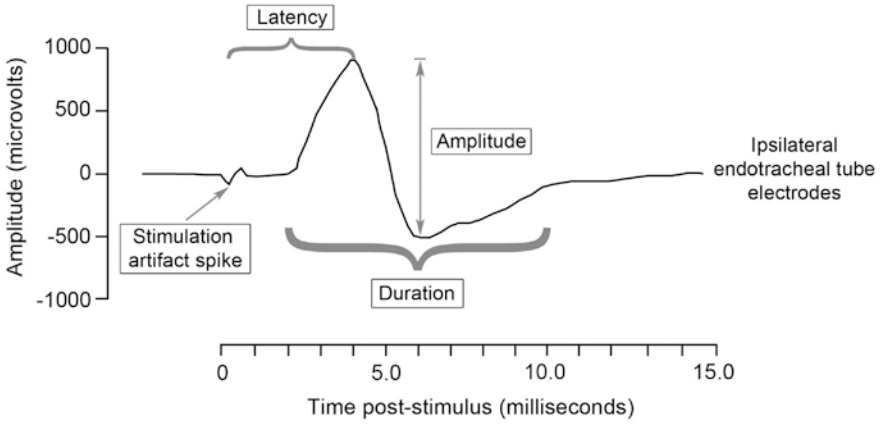

Fig. 11.4 Normative evoked electromyography (EMG) ipsilateral waveform parameters. (Copyright © Gregory W. Randolph [18])

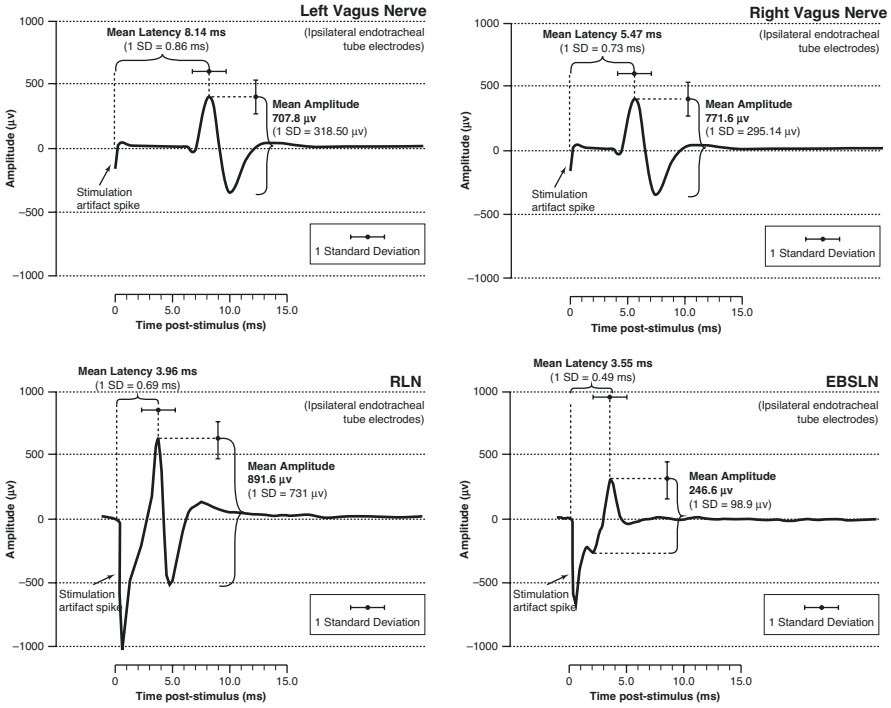

Fig. 11.5 Electromyography (EMG) recordings of left and right vagus nerve, pooled RLN, and pooled EBSLN illustrating normative waveform with normal latency and amplitude. (Copyright © Gregory W. Randolph [43])

Evaluation of Equipment Malfunction

In order to evaluate the reliability of the IONM setup, the laryngeal twitch response can be used by stimulation of the ipsilateral and contralateral vagus nerve. Presence of a twitch reflex confirms that the stimulating side of the equipment is functional. Malfunctioning of the recording side of the equipment usually occurs due to improper tube positioning, inadequate current, presence of blood in the field, or use of paralytic agents. These should all be ruled out before considering a true LOS.

True Loss of Signal

In order to be considered a true LOS, three conditions must be satisfied:

1. Presence of a satisfactory EMG with amplitude >500 µV at the beginning of IONM
2. No or low response on the EMG with stimulation at 1–2 mA in a dry field (i.e., 250 µV or lower)
3. Absence of laryngeal twitch and/or glottis twitch on ipsilateral vagal stimulation

Troubleshooting a LOS

Using a consistent LOS algorithm can help reduce the incidence of false negative prognostic errors. Figure 11.6 describes an algorithm published by the INMSG [32]. The first test to evaluate is whether a laryngeal twitch is present or not. If a twitch is present and contralateral vagus stimulation is absent, check for equipment issues including endotracheal tube position and interface with EMG device. It is recommended to stimulate the vagus nerve as the anesthesiologist repositions the ETT.

If a laryngeal twitch is absent, this could represent an issue with the stimulation side of monitoring. Ensure a dry field and test the probe on muscle. If the stimulator is working, the contralateral vagus nerve should be tested to determine true LOS vs. other etiology.

False Negative vs. False Positive Results

False positive errors occur when there is LOS intraoperatively but the nerve is functional postoperatively and are more common than false negative errors. False negative errors occur when there is a positive signal with the stimulation of the RLN but

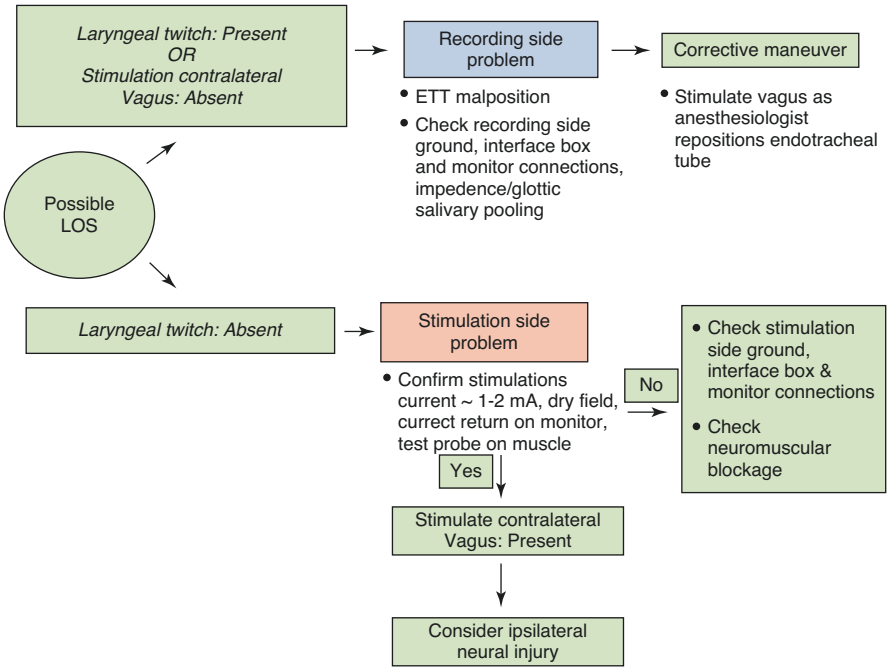

Fig. 11.6 Troubleshooting algorithm to determine presence of true loss of signal (LOS). (Copyright © Gregory W. Randolph [42])

Table 11.1 Sources of prognostic testing errors

False positive errors (normal vocal cord function postop with LOS during surgery)	False negative errors (postop vocal cord dysfunction despite presence of good intraoperative EMG activity)
Inadequate stimulation due to blood in the surgical field or nerve obscured by fascia	Stimulation of the nerve distal to the location of injury
Equipment malfunction (ETT malposition, grounding electrode misplaced)	Vocal cord paralysis or dysfunction related to a nonneural injury (e.g., arytenoid dislocation)
Long-acting neuromuscular blockade	Injury to the nerve after the final stimulation occurred (e.g., during closure)
Vocal cord paralysis with very early recovery before postoperative laryngoscopy is performed	A posterior branch injury may not be detected by IONM
	Delayed neuropraxia from edema

EMG electromyography, *LOS* loss of signal

there is postoperative vocal cord dysfunction/paralysis. Table 11.1 reviews causes for these errors [48]. Surgeons should carefully assess for each scenario when making decisions about moving onto the contralateral side.

Management Strategies

As mentioned before, IONM can be used to prognosticate the postoperative status of the RLN. If there is concern about the functionality of the nerve or loss of signal after dissection of the initial side, the surgeon should first go through the entire troubleshooting algorithm to determine if there is a true LOS. If that is the case, the contralateral surgery should be delayed unless the patient has high-risk disease or a second anesthesia experience would entail grave risk. If the surgeon chooses to proceed with the surgery, it is imperative that the patient is adequately counseled regarding tracheostomy [32].

Staged Surgery

Staging of contralateral surgery is recommended if a true LOS occurs (unless high-risk disease) and laryngoscopy is performed postoperatively to evaluate vocal cord function. The recovery of laryngeal function is the predominant factor in determining the timing for completion surgery. Several studies have shown that neuropraxic injury usually recovers in 2–6 months [49–51]. Laryngoscopy should be performed initially between 2 weeks and 2 months after surgery and then every 4 weeks during this time period [11]. In patients undergoing surgical treatment for thyroid

carcinoma, there is no impact on oncological outcomes if completion surgery is performed within 6 months, as long as there is no residual tumor or distant metastasis [52–54].

Importantly, recovery of nerve function indicates that completion thyroidectomy would be safe but does not necessarily mean that it needs to be performed. Indications for surgery should be re-evaluated and discussed with the patient to determine if surgery is still necessary. If the nerve does not recover function within 6 months, further management, including the role for observation, radioactive iodine, or even external beam radiation, should be carefully considered within a multidisciplinary setting.

Recent Advances in IONM and Future Directions

Continuous Vagal Monitoring

Continuous IONM (CIONM) performed with a vagal nerve electrode is a new format of IONM in which constant, real-time intraoperative EMG data is obtained from vagus and RLN circuitry. This technology allows the surgeon to get continuous feedback regarding the functional status of the nerve and make corrections immediately if there appears to be damage to the nerve. CIONM is delineated comprehensively in the following chapter.

Superior Laryngeal Nerve (SLN) Monitoring

Injury to the external branch of the SLN (EBSLN) causes cricothyroid muscle dysfunction and in turn alters vocal projection affecting the ability to produce higher registers of the voice. These voice changes are subtle but significantly impact professional voice users. IONM of the EBSLN allows for stimulation and identification of all EBSLNs including the 20% subfascial EBSLNs [55]. The application and utility of intraoperative monitoring of SLN is discussed in detail in Chap. 13.

Intraoperative Identification of Nonrecurrent Laryngeal Nerve

A nonrecurrent laryngeal nerve (NRLN) is an uncommon anatomical variant of RLN. It is more common on the right side (0.5–1%). Left-sided NRLN is extremely rare (0.04%) and is associated with situs inversus. While NRLN does not have functional implications, when its presence is not identified, it can add to the risk for intraoperative neural injury. At present, preoperative identification of NRLN through

imaging studies is not reliable. An IONM-based algorithm has been applied to detect the existence of NRLN prior to the dissection. The presence of a positive EMG response to proximal stimulation of the vagus nerve at the superior border of the thyroid cartilage combined with the absence of an EMG response to distal stimulation of the vagus nerve below the inferior border of the fourth tracheal ring reliably identifies all NRLNs [56, 57]. A NRLN has similar electrophysiological parameters (amplitude, latency, and threshold) as that of a RLN. Some researchers have evaluated the latency values of NRLN and suggest that a latency of less than 3.5 ms strongly favors the presence of a NRLN [58]. This concept needs to be further evaluated as future studies may be able to establish a cutoff value for latency as a definitive indicator of NRLN.

Conclusion

To recapitulate, the actual benefits of IONM are perceived only when it is performed as per established standards and when the functional data, i.e., the electrophysiological information obtained by IONM, are accurately interpreted. Additionally, IONM entails a learning curve and extra cost. However, the beneficial information provided by IONM offsets the additional cost and the time needed for learning. The information provided by IONM aids in intraoperative nerve identification, in surgical decision-making regarding nerve management, and in avoiding bilateral nerve injury.

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Chapter 12
Continuous Neuromonitoring of the Recurrent Laryngeal Nerve

Marcin Barczyński and Rick Schneider

Introduction

Surgery of the thyroid gland, and especially total thyroidectomy, is always associated with the risk of transient or permanent paralysis of the laryngeal nerves (the recurrent laryngeal nerves or external branches of the superior laryngeal nerves) and postoperative hypoparathyroidism (transient or permanent).

For years now, the importance of recurrent laryngeal nerve (RLN) visualization in the course of thyroid operations has been stressed; it reduces the incidence of nerve injuries and constitutes the accepted standard for safe operative technique [1–3]. In recent years, intraoperative neuromonitoring (IONM) of the laryngeal nerves has been gaining an ever-increasing acceptance as a method that supplements visualization of the nerve to evaluate its functional integrity during the surgery [4, 5]. Today, it is believed to be a valuable method not only when employed by younger surgeons with less experience but also when utilized by those with many years of experience in thyroid surgery and profound knowledge of the surgical anatomy [4, 6].

In 2011, the International Neural Monitoring Study Group published guidelines addressing the recommended standards of RLN IONM. Subsequent guidelines have addressed the standards of neuromonitoring of the external branch of the superior laryngeal nerve (EBSLN), staging bilateral thyroid surgery with monitoring loss of signal, and optimal RLN management for invasive thyroid cancer [7–10].

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M. C. Singer, D. J. Terris (eds.), *Innovations in Modern Endocrine Surgery*,
https://doi.org/10.1007/978-3-030-73951-5_12

At present, three types of intraoperative neurophysiological laryngeal nerve monitoring are distinguished:

1. Intermittent RLN neuromonitoring (i-IONM)
2. Continuous RLN neuromonitoring (c-IONM)
3. Neuromonitoring of the EBSLN

In this chapter, an outline of the most current approach to c-IONM of the RLN during thyroid surgery is provided with special emphasis put on potential of this method in improving outcomes of thyroid surgery.

Rationale for Use of c-IONM

Intermittent IONM remains the most commonly employed method for confirming visual RLN identification as well as for neural mapping to identify the nerve before it is exposed in the surgical field. This ability is of particular importance in secondary procedures and operations for recurrent disease. i-IONM allows for prognostication of postoperative nerve function and in cases where there is loss of signal (LOS) – for determining the character of an injury and precise location of the damaged site. It also allows for modifying the surgical plan, i.e., for postponing the surgical treatment of the contralateral side (staged thyroidectomy) if during the procedure LOS occurs [9]. However, there are significant limitations to the benefits of i-IONM. Most importantly, this form of neuromonitoring only allows recognition of RLN injury once it has already occurred. It does not provide any data warning or an impending nerve injury.

As many of RLN injuries are a result of an accumulation of micro-injuries, related to intraoperative manipulations and traction, impending neural injury can only be identified based on real-time and continuous electrophysiological neural data analysis. This crucial information is the significant advantage provided by c-IONM. It allows the surgeon to detect the imminent RLN injury in the course of surgery (with the most common mechanism being traction), correct the surgical maneuvers causing the neural distress, as well as verify recovery of RLN function following intraoperative decrease or loss of EMG signal [9, 11, 12]. Hence, the c-IONM technique aids in preventing, rather than just diagnosing, RLN injury.

Standardized Approach to c-IONM

The equipment to perform the c-IONM technique generally consists of a multichannel EMG system, EMG display, sensing endotracheal surface electrode, handheld stimulation probe, and temporarily placed vagus electrode.

For safe and reliable use of a vagus electrode, the following steps should be followed [7, 11–15]:

- Access the vagus nerve (VN) within the carotid sheath before exposing the thyroid by the anterior (midline, as for primary benign thyroid surgery) or lateral (between sternohyoid and sternocleidomastoid muscle, as for huge thyroid goiter, and redo procedures) approach.
- VN stimulation by handheld stimulation probe prior to vagus electrode placement in order to test its integrity and function. A negative VN stimulation response should lead to using the troubleshooting algorithm described for IONM.
- Gentle 360° dissection of a small segment of the VN at the point where the nerve was previously stimulated. It is important to avoid nerve devascularization during its mobilization (Fig. 12.1).
- Initial vagus stimulation by 1 mA and 1 Hz and system calibration with establishment of an adequate initial baseline. The "baseline" reference amplitude must be ≧500 μV during initial calibration to guarantee a stable and reliable EMG signal. Sufficient amplitude values allow for reliable calculation of latency, as well as permit a tolerance range for dissection-related alterations heralding impending nerve injury.
- Initiate c-IONM, utilizing a timeline of the values of amplitude and latency. This monitor should also display the changes of these values over the course of the surgery. It is possible to set an audible and visual alert when threshold levels are exceeded, to help warn the surgeon of risky maneuvers.
- RLN identification and its further dissection are performed in the manner identical to that of i-IONM, using the handheld stimulation probe.

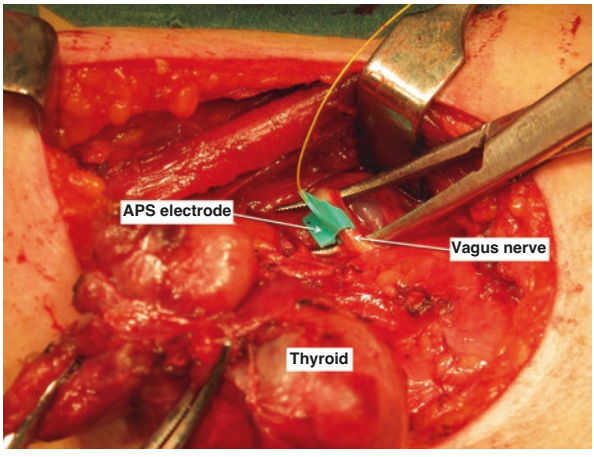

Fig. 12.1 A left-sided vagus nerve is circumferentially dissected (360°) over a short stretch of 1.0 cm, and a 3 mm electrode is placed around it

Interpretation of c-IONM EMG Data

Impending Neural Injury

The skillful use of c-IONM requires experience and observation of the EMG screen to facilitate the interpretation of clinically relevant quantitative EMG signals and to differentiate from "normal" EMG tracings (Figure 12.2a). Adverse "combined" EMG events with specific concordant signal changes in both amplitude and latency, defined as more than 50% decrease in amplitude with more than 10% increase in latency from baseline values, appear to be indicative of impending nerve injury [13]. In a series of 102 patients, combined events had a positive predictive value of 33%, had a negative predictive value of 97%, and were reversible in 73% [16]. Recently, it was shown in 788 patients (1314 nerves at risk) that immediate reaction by withdrawing nerve tension prevented progression to LOS in 80% (63/77 patients) of combined events [17]. An analysis of 101 patients undergoing c-IONM showed that EMG events resolved in 68% of cases (13/19) after cessation of the provoking surgical maneuvers and change in dissection strategy [18]. Most recently, a study of 455 continuously stimulated nerves at risk revealed that the immediate release of retraction successfully preserved the nerve function in all cases with impending injury [19].

This electrophysiological correlate of impending nerve dysfunction can be structured into two phases of neuroanatomical changes: (I) sequential decrease of amplitude as a reduction of the number of functional neurofibers followed by (II) a further decrease in amplitude and increase in latency indicating an additional increase of time interval to vocal muscle action by continued RLN traction. Utilizing c-IONM enables the surgeon to recognize phase 1. This should result in immediate release or cessation of the surgical action to avoid proceeding into phase 2 (impending nerve injury) [11, 12, 20].

Artifact

Periods of minor decrease or increase of amplitude or latency alone may occur more than once during c-IONM. Repetitive increases or decreases in both amplitude and latency may be artifactual, believed to arise from malrotation of the endotracheal tube or tracheal shifting resulting in impaired contact between the recording electrodes and vocal cord. Bipolar forceps coagulation can also cause confusion because of the temporary loss of EMG recording that it causes. Poor VN stimulation is a third scenario that can lead to marked signal artifact. Dislocation of the vagus electrode may occur after inadvertent pulling on the conduction wire. Alternatively, a mismatch between the size of the VN and the electrode may result in poor stimulation characteristics. "EMG storm," with repetitive temporary loss of EMG recording followed by increased amplitude values, is produced by poor vagus contact of an

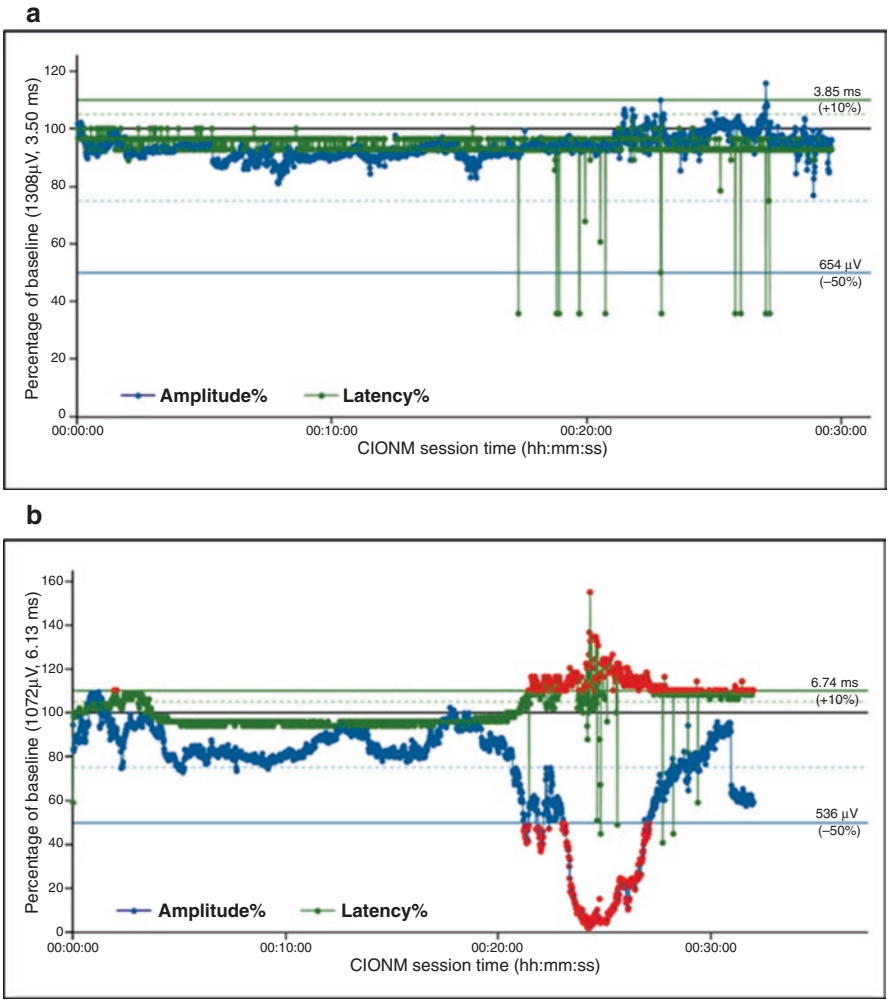

Fig. 12.2 Examples of EMG tracings during continuous intraoperative neural monitoring (nerve amplitude and latency depicted in blue and green). (**a**) "Normal" EMG tracing in an uneventful case, indicating normal vocal cord function. (**b**) Temporary global LOS type 2 (amplitude decrease to <100 µV) traction-caused injury, preceded by combined events (decrease in amplitude <50% with increase in latency >110% relative to baseline) with recovery of amplitude to >50% of baseline, indicating normal vocal cord function. (**c**) Persistent global LOS type 2 traction-caused injury, preceded by combined events without intraoperative recovery of EMG signal, indicating a >70% risk of postoperative vocal cord palsy. (**d**) Persistent segmental LOS type 1 (amplitude decrease to <100 µV) heat-caused injury without intraoperative recovery of EMG signal, indicating a >100% risk of postoperative vocal cord palsy

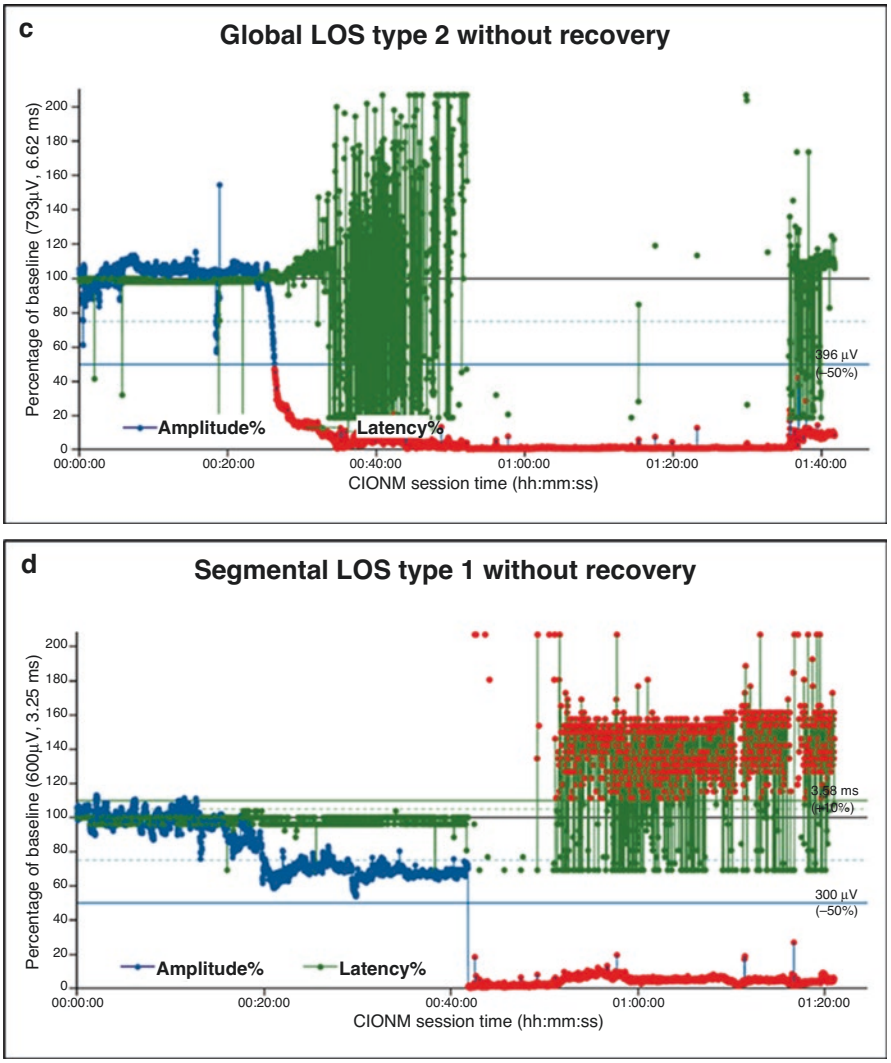

Fig. 12.2 (continued)

excessively large vagal electrode. Typically, in contrast to the EMG changes associated with genuine neural injury, these non-dangerous artifactual signals resolve after repositioning of the vagal electrode or release of the thyroid back into its original position [12–14, 20]. In a series of 102 patients, isolated amplitude or latency changes were not associated with vocal cord paralysis [16].

Signal Recovery

In a recent proof of concept study, nerve recovery was diagnosed intraoperatively after segmental (type 1) or global (type 2) LOS occurred when amplitude rose from <100 μV to >100 μV in 41 patients (41 nerves at risk) [21]. This revealed a correlation between degree of intraoperative amplitude recovery after LOS and postoperative vocal cord function. Signal recovery of ≥50% of nerve baseline amplitude always signified normal postoperative vocal cord function. In contrast, signal recovery of <50% preceded early vocal cord paralysis in all patients with segmental (type 1) injuries and in two-thirds of patients with global (type 2) injuries. This could provide extremely important information for surgeons in planned bilateral surgery. As shown by an international multicenter study of 115 LOS cases at the end of surgery, 80% (92/115 patients) of LOS are caused by traction of the RLN [22]. It has been established in an international multicenter study of 68 patients (68 nerves at risk) that amplitude recovery ≥50% relative to baseline reliably predicted normal early postoperative vocal cord function in all patients after transient segmental LOS or global LOS (Figure 12.2b) [15]. On receiver-operating characteristics analysis, relative and absolute amplitude recovery of 49% and 455 μV (both $P < 0.001$) after segmental LOS type 1 and 44% ($P = 0.01$) or 253 μV ($P = 0.15$) after global LOS type 2 differentiated best between normal and impaired early postoperative vocal cord function. Practically then it may be justifiable to use one amplitude recovery threshold of ≥50% for both types of LOS. This single threshold accurately predicts normal early postoperative vocal cord function after segmental LOS, but may slightly underestimate normal early postoperative vocal cord function after global LOS (the less serious form of nerve injury).

False Positive and False Negative Events

The predictive accuracy of c-IONM at 99.5% is very high and represents a perfect tool for intraoperative decision-making in favor of or against proceeding with contralateral surgery. The low rate of false positives may further decrease the number of unnecessary staged procedures, in particular when the concept of complete amplitude recovery (>50% of initial baseline) after transient LOS is considered in c-IONM-guided thyroidectomy [17]. Therefore, an extended management algorithm is proposed after LOS during c-IONM in thyroid surgery [23].

Furthermore, c-IONM might further decrease the rate of false negative findings and the risk for potential bilateral vocal cord palsy. This is because it overcomes the fundamental risk of i-IONM not to register transient LOS during thyroid surgery. This weakness of i-IONM could result in a presumed “intact” EMG (but weaker than the initial amplitude) but early postoperative vocal cord palsy.

Staged Thyroidectomy with c-IONM

Since it is known that 95% of patients with segmental LOS or 48% of patients with global LOS have impaired early vocal cord function, it is not advisable to wait longer than 20 minutes to assess if a nerve's amplitude recovers >50% or more (Fig. 12.2c and d) [9, 15, 21]. In most cases when a LOS persists or the intraoperative recovery of amplitude is less than 50% on the first side of a planned bilateral thyroidectomy, the decision should be made to not proceed with the contralateral dissection. One should opt for a staged procedure in an effort to protect patients from bilateral RLN paralysis [12, 19, 23–27]. Based on the predominant and overwhelming consideration of nerve recovery, optimal timing of completion surgery is less than 3 days or greater than 3 months when attempting to minimize the risks of completion thyroidectomy [5, 9, 28–30].

If the RLN injury does not recover within 6 months of the initial surgery, it is important that the further management plan incorporates a multidisciplinary approach. If completion surgery is judged to still be necessary, it is imperative to explicitly educate the patient and medical endocrine team regarding the possibility of tracheotomy and the need for experienced tertiary surgical care [9, 27, 31].

Safety of c-IONM

The safety of c-IONM has been addressed in multiple studies [12, 32–35]. Besides a few anecdotal reports of local injuries or cardiac events during c-IONM [18, 36, 37], several large studies have shown no evidence of adverse events related to circular dissection or repetitive stimulation of the VN [38]. As shown in animal experiments, a current of 1 mA used for c-IONM is believed to account for the absence of concomitant or subsequent adverse VN effects such as headache, numbness, arrhythmias, bradycardia, bronchospasm, or nausea [13, 16, 39–44]. As established in a proof of concept study, c-IONM caused a predominance of parasympathetic activity, which was not countered by an increased sympathetic activity [45]. The increased parasympathetic tone did neither impact cardiac or hemodynamic parameters nor the level of proinflammatory cytokine TNF-α [46].

By adhering to the standards of neural monitoring, including gentle vagus and recurrent nerve management, there is no evidence that c-IONM by itself does harm. Even older patients with advanced AV block and/or a pacemaker can be monitored safely with c-IONM [38, 47].

c-IONM vs. i-IONM

As c-IONM is still early in its adoption, limited studies comparing it with i-IONM, in regard to outcomes, have been published. Schneider et al. recently reported an observational study comprised of 1526 patients who underwent thyroid surgery for

benign disease, 788 (1314 nerves at risk) using c-IONM and 738 (965 nerves at risk) with i-IONM. With c-IONM, 63 of 77 (82%) combined events were reversible during the operation. No permanent vocal fold palsy occurred in the c-IONM cohort, whereas four unilateral, permanent vocal fold palsies (0.4%) were diagnosed after i-IONM [17]. The same group of researchers has shown similar results with their pediatric experience [47].

Future Perspectives

C-IONM appears to have the ability to overcome the major disadvantage of the i-IONM [48]. While i-IONM helps to detect injury only after it occurs, the c-IONM format has a potential to prevent neural injury. Recent standardization of the IONM technology has made this technique mature and easy to apply in clinical practice. Prospective and multicenter studies are needed to provide more solid evidence for the benefits of this technology and change the current practice of RLN management in thyroid surgery. This change of paradigm is likely to happen based on mutual feedback of surgical expertise supported by novel technology.

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Chapter 13
Neuromonitoring of the Superior Laryngeal Nerve

Andre S. Potenza and Claudio R. Cernea

Introduction

The external branch of the superior laryngeal nerve (EBSLN) is at risk whenever dissection of the superior pole and ligation of the superior thyroid vessels (STV) are carried out during thyroid and parathyroid operations. The EBSLN is the sole motor nerve to the cricothyroid muscle (CTM), and surgical injury results in lowered voice fundamental frequency, lowered voice projection, fatigue, and failure to produce high-frequency sounds.

Even though the role that EBSLN dysfunction plays in the myriad of vocal changes reported after thyroid surgery is not clear-cut, singers and people making professional use of their voice, such as teachers, lawyers, and broadcasters, can be significantly harmed by the subtle vocal changes that can arise. However, EBSLN injury poses a threat to all patients undergoing thyroid operations as the perception of an abnormal or transformed voice impairs quality of life and decreases general health in a number of ways [1]. The rates of injury of this nerve in thyroidectomy vary in the literature but may be as high as 58% [2].

Intraoperative nerve monitoring (IONM) represents a significant technological advance that enhances the technique of thyroid surgery. It has been increasingly integrated into surgical practice as a tool that aids in the identification and dissection of the superior, inferior, and even nonrecurrent laryngeal nerves, as it prognosticates ultimate neural function and potentially influences surgical strategies [3–5].

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M.C. Singer, D. J. Terris (eds.), *Innovations in Modern Endocrine Surgery*,
https://doi.org/10.1007/978-3-030-73951-5_13

Injury to the EBSLN and Its Consequences

The cricothyroid joints allow both rotation around the frontal axis and the horizontal sliding of the cricoid cartilage in the sagittal axis leading to posterior displacement of the arytenoids, resulting in lengthening and thinning of the vocal folds [6]. Ultimately, CTM contraction regulates vocal fundamental frequency that clinically translates into voice "pitch" [7].

The perception of EBSLN injury is challenging, as only mild changes of the speaking voice ensue. The singing voice is more severely affected. The voice can become weak, breathy, and monotonous, with compression on the pitch range and inability to achieve high-pitch tasks [8–11]. Patients may complain of weakness, tightness, and increased effort to speak. Aerodynamic measures have shown augmented subglottic pressures and decreased airflow rates following paralysis of the CTM [12]. The diagnostic workup can show laryngeal rotation, with the posterior glottis rotated toward the side of the weakness [8, 9, 12–14]. Abelson and Tucker [15] conceived a model of acute CTM paralysis on four volunteers, through local anesthetic block of the EBSLN, in which they found that such rotation happens dynamically on the course of phonatory activity, mainly because the cricoid cartilage moves as the thyroid cartilage remains fixed. In this model, the aryepiglottic fold was felt to be shortened on the side of the paralysis [15]. Bowing and high mismatch with inferior displacement of the vocal cord on the affected side [8, 10, 13–16], as well as vocal fold hypomobility, mucosal asymmetrical waveform excursion, and phase asymmetry [10, 13], are also reported as physical examination findings.

Rubin et al. [17] proposed that vocal fold hypomobility during fatiguing repetitive phonatory tasks would diagnose EBSLN palsy. However, when there is only mild vocal fold lag, variable degrees of compensation by the unaffected muscles can make hypomobility patterns unreliable to reveal EBSLN dysfunction, as reported by Heman-Ackah and Barr [18] in a study comparing clinical scenarios, laryngeal findings, and laryngeal EMG. Mendelsohn et al. [19] also reported on phase asymmetry and described a videostroboscopic pattern of vocal cords "dashing against each other."

In contrast to these studies, Roy et al. did not report consistent patterns of rotation, nor evidence of vocal fold hypomobility [12, 20]. Three literature reviews agree that there are no pathognomonic laryngeal findings to precisely diagnose EBSLN paralysis [21–23]. The clinical manifestations can be easily overlooked and are affected by a variable degree of nerve impairment. Diagnosis is made even more challenging by coexisting RLN dysfunction, variability in the cricothyroid joint tolerance for sliding movement, direct surgical injury to the CTM, compensatory action of other intrinsic muscles, laryngeal fixation from scarring, and the inconstant interconnections between laryngeal nerves [21, 24–27]. The most precise method to assess EBSLN dysfunction is a laryngeal EMG [8, 10]. However, this is invasive, technically difficult, and highly dependent on the operator's experience.

Due to the difficulty with diagnosis, the definite incidence of EBSLN damage during thyroid and parathyroid injury is unknown, and the rates diverge with the methods relied on to diagnose injury. When laryngoscopy and voice analysis are used, the reported incidence ranged from 0% to 6% [28–31]. When EMG was added to the evaluation process, higher rates were reported and reached 58% [2, 13, 32–35].

Fundamentals of EBSLN Preservation: How It Was Done Prior to IONM

Throughout the history of endocrine surgery, a variable degree of concern regarding preservation of the EBSLN is noticeable. The EBSLN has always been given minimal attention as compared to that devoted to the RLN. In 1951, Moran and Castro [36] suggested that voice impairment that was unjustified by RLN injury could be caused by harm to the somewhat neglected EBSLN. They purposely traumatized the EBSLN with a clamp when operating on eight consecutive adenomatous goiters and noticed that in all cases immediate postoperative voice changes emerged. The authors eventually suggested that mass ligatures of the superior pedicle of the thyroid should be avoided [36].

Injury of the EBSLN occurs by transection, clamping, ligature entrapment, stretching, thermal damage, or nerve ischemia [33, 34, 37]. The key to safeguarding the EBSLN is a complete knowledge of the anatomy of the superior thyroid pole area. For this reason, one of the authors (CRC) and many others have proposed classification schemes to determine anatomical landmarks and to outline the relations with the superior thyroid vessels. All of these systems ultimately focus on EBSLN topography and its correlated risk of injury.

Anatomy The EBSLN runs lateral to the thyroid cartilage along the pretracheal fascia and superficial to the inferior pharyngeal constrictor muscle (IPCM) and travels to the CTM parallel to the superior thyroid artery (STA). Near to the lower margin of the thyroid cartilage, it is usually covered by muscle fibers of the IPCM [28, 38–40]. The nerve then usually crosses the STA posteriorly as it approaches the superior thyroid pole and sits medial to the artery in the majority of cases [40]. It is usually encountered within the sternothyroid-laryngeal triangle described by Moosman and DeWeese [41], demarcated by the sternothyroid muscle superiorly, the thyroid and cricoid cartilages with the cricothyroid and pharyngeal constrictors medially, and the retracted upper thyroid lobe laterally and inferiorly (Fig. 13.1) [41].

Cernea et al. [42] proposed their system in 1992. It categorizes the topography of the EBSLN in relation to the superior pole of the thyroid or the superior thyroid vessels, as follows:

- Type 1: the EBSLN crosses the superior vessels more than 1 cm above the edge of the superior pole.
- Type 2a: the EBSLN crosses the vessels within 1 cm above the upper limit of the superior pole.

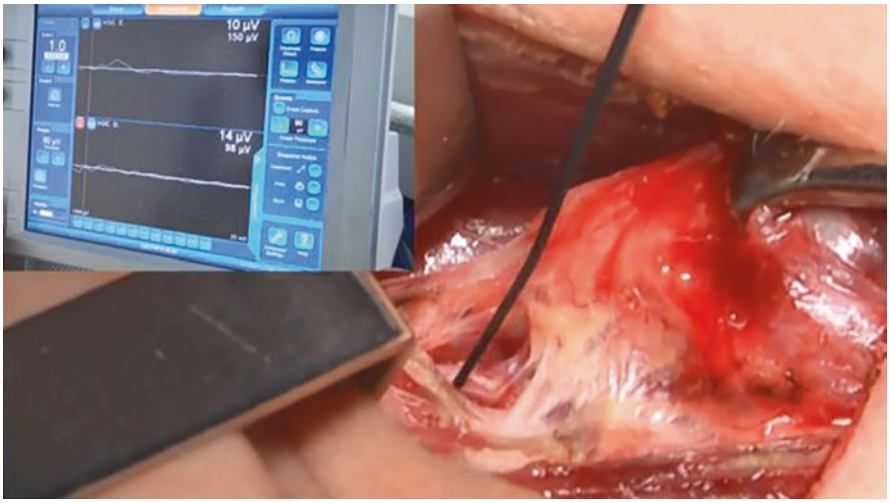

Fig. 13.1 A right-sided EBSLN is shown being stimulated to with the neuromonitoring probe

- Type 2b: the nerve curves, in its way to the CTM, below the upper edge of the superior pole. This position displays the greatest risk of injury and was described by the author in 20% of the subjects in a cadaveric series, in 14% of operated patients with small lobes, and in 54% of patients with very large goiters [42, 43].

A comparable classification was later proposed by Kierner et al. [44] who added a fourth category. In Kierner's type 4 EBSLN, the nerve travels dorsally to the superior thyroid artery and crosses its branches immediately above the upper pole of the thyroid gland [44].

Whereas these two authors undertook cadaveric dissections, Friedman et al. [39] reported their experience in thyroid operations in a retrospective study with 884 patients and over a thousand EBSLNs examined. They offered a scheme based on the relationship between the descendent course of the trunk of the EBSLN and the IPCM:

- Type 1: the EBSLN descends its entire course superficially and laterally to the IPCM until it reaches the CTM.
- Type 2: the nerve deepens into the lower portion of the IPCM, being partially covered by its fibers.
- Type 3: the nerve runs its whole course covered and protected by the IPCM. In this particular situation, the nerve cannot be visually identified in the operative field, but can be electrically mapped out through IONM [39].

As the basis for a third system, Selvan et al. [45] carried out a prospective study of 35 total thyroidectomies with 70 EBSLNs being mapped through recorded compound muscle action potentials and EMG. The authors proposed a new classification based on the superior thyroid vessels and the cricoid cartilage as landmarks:

- Type 1a: the nerve is located within 1 cm of the entry of the vessels into the gland, either anterior or between its branches and within 3 cm from the cartilage.
- Type 1b: the nerve is posterior to the vessels, but within 1 cm of the entry of the superior thyroid vessels in the gland. This is the grade that poses the greatest risk of injury in this nomenclature.
- Type 2: the nerve is located within 1–3 cm of the entry of the superior vessels into the gland or within 3–5 cm from the cricoid cartilage.
- Type 3: the nerve is between 3 and 5 cm of the entry of the vessels or more than 5 cm from the thyroid cartilage [45].

Multiple factors seem to influence the likelihood of successful identification and presentation of the nerve. Cernea et al. [35] showed in a prospective randomized trial that there was significant difference in the rates of EBSLN paralysis that occurred between operations performed by a senior surgeon versus those done by a resident under supervision. This suggests that the surgeon's experience impacts the risk of EBSLN injury. They also proposed that risk of EBSLN injury is proportional to the size of the goiter requiring surgery. When the gland is markedly enlarged, the superior pole seems to occupy a higher position and is more closely related to the EBSLN's descending course [43]. Other groups have found similar associations between larger goiters and risk of EBSLN injury [46–48]. In a retrospective study by Ravikumar et al. [46], 93% of EBSLNs were found by visual identification alone. They found that large goiters are more likely to influence the likelihood of successful identification and preservation of the nerve.

Nerve Identification We believe that visual identification of the EBSLN should be attempted in all cases. This can be successfully achieved in large percentage of patients.

Although there is consensus that mass ligatures of the STV must be avoided, distinct approaches have been described:

1. Individual ligature of the branches of the superior thyroid vessels, as distal and as close to the thyroid capsule as possible, without the need to visually identify the nerve [31, 49]
2. Attempting visual identification of the nerve before the ligature of the superior pole [47, 48, 50–52]

Studies supporting both of these approaches have been published. However, it does seem that the preponderance of evidence establish the value of identification to reduce the likelihood of nerve injury.

IONM and EBSLN Preservation

Since concomitant EBSLN monitoring can be achieved with the same equipment as utilized for RLN IONM, EBSLN IONM has also been progressively embraced by thyroid and parathyroid surgeons [32]. A web-based survey sent to surgeons with a

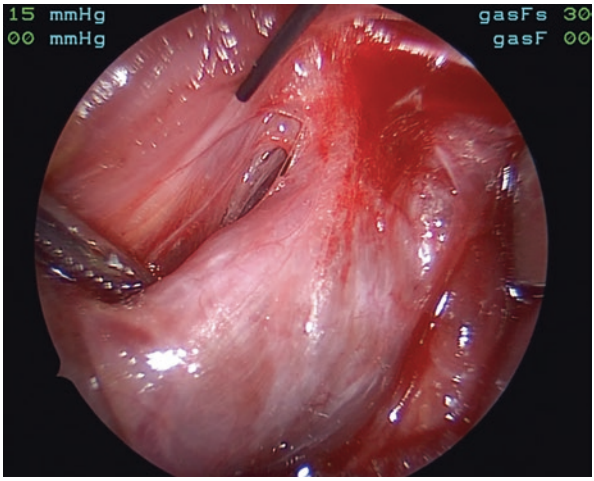

Fig. 13.2 Neuromonitoring of the EBSLN can be performed during minimally invasive or video-assisted thyroidectomy. Here a left-sided EBSLN is demonstrated medial to the superior pedicle during a MIVAT procedure

known interest in endocrine surgery found that EBSLN IONM was used by 68% of high-volume surgeons in 2014, and 93% of respondents agreed that IONM identification of the EBSLN was necessary when operating on voice professionals [58].

All means of electrostimulation provoke a brisk CTM contraction that is easily observed in the surgical field. This is the key feature of EBSLN IONM. Furthermore, IONM allows one to pinpoint the nerve and to record either glottic thyroarytenoid muscle activity over dedicated endotracheal tubes [3, 32, 54] or direct CTM responses by needle electrodes [56, 57, 59]. EBSLN-elicited action potentials of the thyroarytenoid muscle are assumed to be mediated by a number of anastomotic interconnections between the RLN and the EBSLN, and virtually all cases are amenable to monitoring as long as preoperative EBSLN function is intact and proper equipment setup is implemented (Fig. 13.2) [32, 54].

Benefits of IONM

Improvement of EBSLN Identification and Preservation with IONM Electrical stimulation helps to map out the trajectory of both laryngeal nerves and is even important in Cernea's type 1 and Friedman's type 3 EBSLNs that run deep to the IPCM fibers and are as prevalent as 20% [39]. Although the nerve is deep and protected in these situations, IONM allows electrical plotting of its course.

A number of studies have reported excellent rates, some over 90%, of unassisted visual identification of the EBSLN [47, 48, 51]. However, many other prospective studies in which rates of EBSLN visual recognition were noticeably lower in the arm without electrostimulation diverge from these findings. Moreover, fibers that are only visually identified, but not stimulated, may not be the actual nerve, as other nonneural structures such as tendons and muscle fibers could be mistaken for the

external branch [45]. These researchers report much higher rates of identification when IONM is employed [29, 34, 53, 55, 59, 61]. Dionigi et al. [55] visually identified 42% of the EBSLNs in 72 video-assisted thyroidectomies under a 30° 5 mm endoscope, while 84% were found with the aid of IONM ($p < 0.05$). Similarly, Lifante et al. [59] found only 21% of the nerves in the unmonitored arm of mini-incision thyroidectomies under local anesthesia versus 66% in monitored patients ($p = 0.03$). Similarly, Barczynski et al. [29] randomized 210 patients to undergo thyroidectomy without or with nerve monitoring and reported a rate of EBSLN identification of 34% versus 84%, respectively ($p < 0.01$). With limited surgical field exposure, as in robotic [62] video-assisted [55] and mini-incision thyroidectomies [56, 59], IONM is clearly useful in providing, at least, electrophysiological identification of the EBSLN.

In addition to identifying and confirming a structure as the EBSLN, probe stimulation can preclude the presence of the nerve within the pedicle to be clamped and divided. A true negative stimulation confirmed by both the lack of electromyographical response and absent CTM twitch following probe stimulation of the tissue to be divided must be confirmed before cutting through vessels and connective tissue around the superior pole [32]. Also, electrostimulation can be eventually used to map out the site of injury should transection or EBSLN entrapment occur and loss of signal (LOS) arise.

Neuromonitoring Technique, Equipment, and Setup The International Neural Monitoring Study Group (INMSG) published in 2013 guidelines for monitoring the EBSLN [32]. The algorithms present in this document offer a standardized approach for optimal and efficient neural monitoring and system troubleshooting. Overall, the technique of EBSLN monitoring relies on two major maneuvers: (1) true positive responses occur when brisk CTM contraction (or glottic EMG waveform) is seen following EBSLN stimulation with the neural probe at 1 mA, and (2) true negative stimulus occur when neither CTM contraction nor EMG glottic responses appear when the pedicle to be divided is stimulated with 1–2 mA [32].

Due to its availability, safety, and simplicity, monitoring with endotracheal tubes with surface-based electrodes is currently the most commonly employed method for both EBSLN and RLN IONM. The standards for anesthesia, tube placement, and confirmation of tube position are the same for both nerves [3]. Neuromuscular blocking agents must be avoided or reversed as monitoring begins, and the use of lubricants over the tube should also be omitted. Proper tube positioning is crucial and should be confirmed by direct visualization and by the recording of spontaneous EMG activity (represented as waves of respiratory variation on the screen) that arise when a more superficial anesthetic level is allowed. The use of monitors that provide graphic representation and recording of action potential waveforms is preferred over the simpler sound alarm-based devices [3].

The equipment is then set up to apply electrical stimulation through either monopolar or bipolar probes, with a pulsatile stimulus of 100 μs duration at 4 Hz and a current of 1–2 mA. The current can be brought down or up throughout the case as needed. Higher currents deliver a broader area of depolarization, thus being useful

when one wants to rule out the presence of neural tissue and rely on a true negative response, as lower currents on the other hand allow one to pinpoint the exact location or the path of the nerve.

EMG Recording and Postoperative Documentation Electrical stimulation of the EBSLN provokes an action potential with a recordable waveform that is morphologically distinct from vagus nerve and RLN waves. Data also suggests that all three nerves show unique normative parameters of latency and amplitude of response [60, 63, 64]. In a study of prospective IONM recordings of 72 consecutive thyroid operations, nonartifactual EBSLN waveforms that were either biphasic or triphasic were registered, with short latency and a mean amplitude of about 270 μV. Mean EBSLN amplitudes of response were roughly 1/3 of RLN amplitudes [60]. These parameters are concordant with Barczynski et al. and Dionigi et al. reports on normative data [29, 33].

In contrast with routine IONM of the RLN, in which the recording of a robust positive VN response predicts normal neural function by the end of the case, EBSLN's functional integrity can only be registered if stimulation is applied cranially to the uppermost-ligated stumps of the STV in the surgical field [33, 34]. Dionigi et al. [33] proposed that the algorithm for IONM should include initial (*S*1) and post-dissection (*S*2) EBSLN stimulations, as these maneuvers may serve the purpose of documentation that the nerve has been identified and preserved.

Conclusion

EBSLN injury can cause significant vocal dysfunction for both professional and nonprofessional voice users. Historically, many surgeons have attempted to minimize the risk of damaging the EBSLN by simply avoiding it. However, as with the RLN, identification of the nerve seems to provide patients with significantly better voice outcomes. IONM of the EBSLN serves as a tool to dramatically increase the rate of EBSLN identification and preservation. With time adoption of monitoring techniques of the EBLSN will likely become widely adopted.

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Chapter 14
Advanced Energy Devices

Jina Kim and Quan-Yang Duh

Introduction

Electrosurgery refers to the use of high-frequency electrical current to coagulate and cut tissues. In the modern-day operating room, electrosurgery is practically synonymous with Bovie cautery, which was based on the work of scientist William T. Bovie and neurosurgeon Harvey Cushing. In 1926, Cushing first used Bovie's diathermy unit in the operating room to remove a vascular myeloma from the head of a 64-year-old patient [1]. Since then, a wide variety of electrosurgical devices have been developed and are used in endocrine surgery today.

This chapter discusses three types of advanced energy devices that have been used in endocrine surgery: bipolar vessel sealing systems, ultrasonic devices, and radiofrequency ablation (RFA). Bipolar vessel sealing systems deliver bipolar current with tissue apposition to coagulate tissue. Ultrasonic devices generate ultrasonic vibration to create heat, coagulating and cutting tissues. Both types of devices have been used in endocrine surgery as an alternative to conventional suture ligation or clipping of blood vessels. More recently, RFA has been applied to treat benign thyroid nodules, microcarcinomas, and recurrent thyroid cancers. RFA transmits high-frequency alternating current in the radio range of frequencies (460–500 kHz) through an electrode to cause focal tissue disruption.

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M. C. Singer, D. J. Terris (eds.), *Innovations in Modern Endocrine Surgery*,
https://doi.org/10.1007/978-3-030-73951-5_14

Bipolar Vessel Sealing Systems

Bipolar vessel sealing systems simultaneously deliver bipolar energy (which denatures collagen and elastin to form a coagulative sealant) and apply pressure by apposing the tines of the instrument [2]. When coagulation is complete, the increase in impedance triggers an automatic interruption of the electrical current, thus minimizing energy dissipation and heat transference to adjacent tissues [3]. LigaSure (Medtronic, Minneapolis, USA) is a well-known bipolar vessel sealing system. With LigaSure, animal studies have shown that the field of tissue injury from thermal spread is up to 4 mm [4, 5]. In studies comparing LigaSure and traditional suture ligation, LigaSure use has been associated with shorter operative time and less transient hypocalcemia in thyroid operations [6–9]. For example, in a 2007 retrospective study of 403 patients who underwent thyroid surgery with either conventional hemostasis or LigaSure, Lepner and Vaasna found that the average operative time was shorter with LigaSure by 25.8 minutes [6]. Shen et al. found similar results in a retrospective study of 234 consecutive patients who underwent thyroidectomy with one surgeon, using either conventional vessel ligation or LigaSure [10].

LigaSure has also been studied in operations for specific thyroid conditions, such as multinodular goiter and Graves' disease. Saint Marc et al. compared LigaSure and conventional hemostasis in 200 consecutive patients with multinodular goiter at their institution: LigaSure use was associated with slightly shorter mean operative time (41.5 vs. 48.9 minutes, $p = 0.001$), but no difference in postoperative complication rates (37% vs. 33%, $p = 0.66$) [11]. In a prospective, non-randomized study of 100 patients undergoing thyroidectomy for Graves' disease, LigaSure again was associated with shorter mean operative time (75 vs. 58 minutes, $p = 0.0001$) and similar complication rates (4% vs. 6%, $p = 0.64$), compared to conventional hemostasis [12].

Although evidence for the use of energy devices in thyroid surgery are predominantly derived from single-center studies, quality improvement initiatives such as the American College of Surgeons National Surgical Quality Improvement Project (ACS NSQIP) have enabled researchers to study complication rates on a population level. In 2019, Siu et al. examined the effect of vessel sealing devices in postoperative hematoma, compared to conventional hemostasis, using the thyroidectomy module of the procedure-targeted ACS NSQIP. In this study of 6522 propensity-matched patients, conventional hemostasis was associated with higher risk of neck hematoma, compared to vessel sealing devices (odds ratio [OR] 2.33, 95% confidence interval [CI] 1.55–3.49, $p < 0.001$). The number needed to treat with a vessel sealing device to prevent one postoperative hematoma was 74. There was no difference in the odds of recurrent laryngeal nerve injury (OR 0.9, 95% CI 0.96–1.01, $p = 0.32$) [13].

Other Vessel Sealing Systems

While the LigaSure brand has been most well studied, other bipolar vessel sealing systems are available in the current market, such as BiClamp 150 (ERBE, Tübingen, Germany), Thunderbeat (Olympus, Tokyo, Japan), and Enseal (Ethicon, Cincinnati,

USA). BiClamp 150 is a system designed specifically for thyroid surgery. Small, single-institution studies have compared BiClamp 150 to conventional suture ligation or other energy devices [14–16]. In one retrospective study of 1156 thyroid operations at a single institution, BiClamp 150 was associated with shorter average operative time and a lower rate of reoperation for hematoma, compared to conventional suture ligation [15]. And when compared to LigaSure in a single-center, prospective study of 86 patients, BiClamp 150 was associated with lower rate of oral calcium supplementation (34.7% vs. 67.5%, $p = 0.002$) and shorter operative time (142 vs. 170 minutes, $p = 0.023$) [16].

Thunderbeat is a hybrid technology that simultaneously applies bipolar and ultrasonic energy to tissue, enabling both vessel sealing and tissue dissection in a single instrument. When Thunderbeat was compared to Harmonic Focus (a widely used ultrasonic device, discussed later in this chapter) in a retrospective study of 761 consecutive patients undergoing thyroid surgery, Thunderbeat cases had similar operative times, estimated blood loss, and length of hospital stay. Thunderbeat was also associated with a lower risk of transient recurrent laryngeal nerve paralysis (OR 0.31, 95% CI 0.13–0.75, $p = 0.009$) [17]. In regard to safety of using Thunderbeat near the recurrent laryngeal nerve, one study used Thunderbeat while performing thyroidectomy with continuous intraoperative nerve monitoring in four piglets. The authors found no adverse electromyography events when Thunderbeat was used at 3 mm or further away from the nerve [18].

Ultrasonic Devices

Ultrasonic surgical devices generate ultrasonic vibration at 55 kHz over a distance of 50–100 μm. This generates heat and friction in tissues to cause protein denaturation [19, 20]. As a result, ultrasonic devices produce less heat and also allow for efficient dissection, as the instrument is able to both coagulate and cut. A comparative study of thermal damage on human peritoneum showed that Harmonic scalpel produced less thermal damage than monopolar cautery, but was similar to that of LigaSure [21]. When bipolar electrothermal energy and ultrasonic energy were compared in porcine blood vessels, mean thermal spread was not statistically significant [5]. In endocrine surgery, it is especially important to minimize thermal spread when dissecting near the recurrent laryngeal nerve, the external branch of the superior laryngeal nerve, and the parathyroid glands.

The Harmonic family of energy devices is the best-known brand in ultrasonic surgical technology. Ultracision CS-14C was the first Harmonic scalpel device for thyroid surgery and approved by the Food and Drug Administration for sealing vessels up to 3 mm in diameter [22]. The Harmonic Focus is a newer device approved for sealing vessels up to 5 mm in diameter. The efficacy of Harmonic Focus has been examined in multiple prospective studies [23–29]. A 2013 prospective randomized study of 778 patients at a single institution showed that use of Harmonic Focus was associated with shorter operative time (79 vs. 125 minutes, $p < 0.001$) and less symptomatic hypocalcemia (3.6% vs. 6.9%, $p < 0.05$), compared to

conventional hemostatic technique [29]. A 2016 meta-analysis by Cannizzaro et al. comparing Harmonic Focus to conventional hemostasis and LigaSure included 14 studies consisting of 2293 patients who underwent total thyroidectomy. The operative time was shorter with the Harmonic Focus than conventional hemostasis (−27.2 minutes, $p = 0.0001$), but the complication rate was similar (OR 0.816, 95% CI 0.471–1.412, $p = 0.467$). Then, comparing LigaSure Precise and Harmonic Focus, the operative times and complication rates were similar [30]. Similarly, in a 2011 single-blinded, prospective study of 90 patients undergoing thyroidectomy who were randomized to bipolar vessel sealing or ultrasonic coagulation, Rahbari et al. found that there was no statistically significant difference in operative time or cost between the two groups [31].

The Harmonic scalpel has also been studied in specific thyroid conditions, such as Graves' disease and multinodular goiter [32, 33]. In a 2008 study, 51 patients with Graves' disease were randomized to use of Harmonic Ultracision scalpel or conventional hemostasis for total thyroidectomy. Use of the Harmonic scalpel was associated with shorter operative time (121 minutes vs. 172 minutes, $p = 0.011$), but similar intraoperative blood loss (69 vs. 79 mL, $p = 0.42$) and similar rate of transient recurrent laryngeal nerve paresis (14% vs. 4%, $p = 0.35$), compared to conventional hemostasis [32].

Challenges, Obstacles, and Misconceptions of Advanced Energy Devices

With any newly introduced surgical innovation, there is always concern that it will be inferior to the traditional technique. In the case of energy devices in thyroid surgery, there have been concerns that use of energy devices without permanent sutures may increase the risk of postoperative hematoma and that use of thermal energy intraoperatively may increase the risk of recurrent laryngeal nerve injury. However, as we discuss in this chapter, studies have shown that energy devices are associated with similar rates of hematoma and nerve injury as traditional suture ligation in thyroid surgery [6–9, 11, 12, 29, 30, 32, 33]. Most endocrine surgeons currently use energy devices alone or as an adjunct to suture ligation. And as current surgical residents increasingly learn to use energy devices in training, we expect that energy devices will remain an essential part of the surgeon's toolbox in the future [34, 35].

However, a lack of basic understanding of energy devices is a major obstacle to using them effectively and safely in the operating room. While surgeons increasingly use energy devices, they are not required to formally learn or document their understanding of energy devices, which has created a significant knowledge gap. For example, when an 11-item multiple-choice exam on surgical energy was administered to 48 leaders within the Society of American Gastrointestinal and Endoscopic Surgeons (SAGES), the median percent of correct answers was 59%. Among the examinees, 31% did not know how to correctly handle a fire on the patient [36]. To

address this knowledge gap, the SAGES initiated the Fundamental Use of Surgical Energy (FUSE) project in 2010 and now offers a formal curriculum on understanding surgical energy devices [37–39].

Energy Devices in Remote Access Thyroid Surgery

In addition to studies of open thyroid surgery, energy devices have also been tested in minimally invasive video-assisted thyroidectomy (MIVAT) and remote access thyroidectomy, where suture ligation is not feasible or practical. There are several published approaches for remote access thyroid surgery, including transaxillary, robotic facelift, and transoral endoscopic or robotic approaches [40, 41]. In a prospective study of 67 patients with a solitary nodule <30 mm undergoing lobectomy via the MIVAT approach, patients were randomized to clip ligation of the superior pole vessels vs. Harmonic scalpel use. In the MIVAT approach, the authors created a 1.5 cm skin incision above the sternal notch, developed a working space by blunt dissection, and used a rigid endoscope to aid thyroid dissection. They found that Harmonic scalpel use was associated with greater cosmetic satisfaction at 1 month postoperatively, although this difference was not significant by 6 months [42]. In another study examining the Harmonic scalpel in 114 patients undergoing endoscopic thyroid surgery via a unilateral axillo-breast approach, minor skin flap hematomas were noted in 3 patients and transient unilateral vocal cord palsy in 5 patients [43]. Rare thermal injury of the skin flap has also been reported when using energy devices in endoscopic thyroid surgery [44]. These studies, albeit from single centers with small cohort sizes, show that energy devices like the Harmonic scalpel can be used safely in endoscopic thyroid surgery.

Future Directions: Radiofrequency Ablation

An emerging field for using energy devices in thyroid surgery is radiofrequency ablation (RFA), which has been applied in treatment of other solid organ tumors [45]. Radiofrequency waves agitate ions as they attempt to follow changes in the direction of the alternating current. Such agitation creates frictional heat around the electrode to produce protein denaturation and cell death [46]. RFA devices have been designed specifically for thyroid applications, with shorter and thinner electrodes and active tips as small as 3.8 mm to allow precise treatment of the target with minimal damage to adjacent tissues. RFA has been shown to be effective in benign thyroid nodules and recurrent thyroid cancer [47–51].

Several institutions across the world have reported their short- and long-term experiences with RFA for benign thyroid nodules. In a 2019 single-center, retrospective study, Guang et al. followed 194 nodules in 103 patients over a mean of 16 months: 50.5% of nodules required a single RFA session, 44.9% 2 sessions, and

4.6% 3 sessions. Nodules were grouped by size as small (≤5 mL), medium (5.1–13 mL), intermediate (13.1–30 mL), and large (>30 mL). The authors found that nodule volume significantly decreased across all nodule sizes, with the greatest reduction in small nodules (volume reduction ratio 98.7% at 24 months). Cosmetic scores increased the most for patients with intermediate- or large-sized nodules [52]. Retrospective studies from other countries have also demonstrated efficacy of RFA in treating benign thyroid nodules [53–55].

RFA has also been used in the treatment of thyroid microcarcinoma and recurrent thyroid cancer with both short- and long-term efficacies [50, 51, 56, 57]. In a retrospective study of 174 patients with isolated, solitary intrathyroidal papillary thyroid microcarcinoma, 94 underwent RFA, and 80 underwent surgery. In the surgery group, three patients experienced complications (two with permanent nerve injury and one with permanent hypoparathyroidism), while no complications were reported in the RFA group. Over 5-year follow-up, one patient in each group developed recurrence [56]. In another retrospective study of 73 patients who underwent RFA or repeat surgery for recurrent thyroid cancer with a maximum tumor dimension <2 cm, 27 were treated with RFA and 46 underwent repeat surgery. The 1- and 3-year recurrence-free survival rates were statistically similar for RFA (96.0% and 92.6%, respectively) and repeat surgery (92.2% and 92.2%, respectively) after adjustment with inverse probability of treatment weights to minimize the effect of selection bias. In addition, after adjustment, hoarseness rates did not differ between RFA and reoperation groups (7.3% vs. 9.0%, $p = 0.812$) [51].

Overall, while RFA has been used extensively in other organs, it is currently a new tool for thyroid tumors. As our understanding of RFA in endocrine surgery evolves, we expect that clinical parameters for RFA use will become established in the future.

Conclusion

Energy devices, such as bipolar vessel sealing systems and ultrasonic shears, are an integral part of modern endocrine surgery. While energy devices do not completely replace conventional suture ligation, they do enable advances in surgical approach such as minimally invasive or remote access thyroid surgery:

- Adequate hemostasis and thermal spread to adjacent structures such as the recurrent laryngeal nerve are two primary concerns regarding use of energy devices in endocrine surgery.
- Bipolar vessel sealing and ultrasonic devices are associated with similar complication rates as conventional suture ligation in thyroidectomy.
- Radiofrequency ablation is an emerging area of interest in endocrine surgery, and it is being studied as an alternative means to treat benign thyroid nodules and thyroid cancer.

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Chapter 15
Parathyroid Gland Fluorescence Imaging

Richard H. Law and Michael C. Singer

The ability to identify parathyroid glands (PGs) is a fundamental component of both thyroid and parathyroid surgeries. Parathyroidectomy relies on identification of these glands to allow the surgeon to assess them for possible pathology and need for excision. In thyroidectomy, PG recognition is the required first step in the multiphase process of parathyroid preservation, needed to minimize the risk of hypoparathyroidism. After their identification, dissection assessment of their viability is then required.

Until recently, all of these abilities depended on the competence of the surgeon. Recently, however, technologies have emerged that appear to provide surgeons with an adjuvant tool for PG identification and preservation. These technologies, which utilize near-infrared imaging (NIRI) with endogenous PG autofluorescence (AF) or with the aid of indocyanine green (ICG), are early in their development, and their precise role in clinical care has yet to be determined. This chapter will discuss some of the nuances and limitations of these intraoperative imaging modalities and their potential future applications.

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M. C. Singer, D. J. Terris (eds.), *Innovations in Modern Endocrine Surgery*,
https://doi.org/10.1007/978-3-030-73951-5_15

The Need for Parathyroid Gland Identification and Assessment of Viability

One of the most common complications of thyroidectomy is postoperative temporary hypoparathyroidism leading to hypocalcemia, with rates of up to 35% [1–4]. The rate of permanent hypocalcemia is lower but still quite high [5–11]. Permanent hypoparathyroidism significantly impacts patients' long-term health and quality of life.

While in the past some surgeons ascribed to the belief that avoiding the PGs during thyroid surgery was the optimal approach to reduce the risk of this complication, today most surgeons believe that identification of the PGs results in improved hypoparathyroidism outcomes. Once identified, proceeding with a "capsular dissection" is most likely to maintain the terminal blood supply to the glands.

In addition to PG detection, in thyroid surgery, assessing the vascular viability of the glands is crucial, as a gland that has been deemed devascularized can be reimplanted. However, the terminal vascular supply of the parathyroid glands is highly irregular and delicate, making dissection quite challenging.

Distinguishing PGs is the cornerstone of successful parathyroidectomy. While preoperative radiologic modalities often can provide precise localization of pathologic PGs, failure to find the abnormal gland(s), and thus cure patients, remains the most common complication of parathyroid surgery. PG recognition can be made more challenging by ectopic positioning, concurrent thyroid disease, or unfavorable body habitus. This can be especially true in the setting of non-localization or four-gland hyperplasia.

Parathyroid Gland Identification and Detection

Historically, the detection and differentiation of the PG from surrounding tissues relied purely on the skill of the surgeon. Knowledge of anatomy and tissue characteristics, including color, was needed to appreciate these small glands. Despite the well-established anatomical relationships for PG identification, certain scenarios make identification particularly difficult, such as very large goiters, reoperative surgery, and/or autoimmune/inflammatory states such as Hashimoto's thyroiditis. The variability in location and vascular supply to the PGs can make their identification and preservation even more challenging [3]. As a result, the rate of parathyroid identification is highly disparate between surgeons and is largely dependent on their training and experience.

While extensive efforts have been put into developing and refining radiology modalities to localize pathologic PGs preoperatively, less attention has been focused on tools to aid in their intraoperative detection. Early efforts in developing a real-time intraoperative method of identifying PGs included radioguided parathyroidectomy with intraoperative scintigraphy, methylene blue (MB) injection, and

aminolevulinic acid (ALA) injection [12–16]. Unfortunately, all of these methods have significant drawbacks.

Dudley was the first to use intravenous administration of MB to identify PGs intraoperatively [17, 18]. After this paper was published, MB injection attained some degree of popularity. However, some potential adverse side effects including neurotoxicity, phototoxicity, pain at the injection site, and nausea were recognized [13, 14, 17, 19, 20]. Fears of these complications, particularly the risk of encephalopathy, led most surgeons to reject this approach.

ALA is another fluorescent molecule that has been used to aid in PG detection in both thyroid and parathyroid surgeries [14, 15, 21–23]. It serves as an intermediate of heme biosynthesis and is a precursor to the fluorescent protoporphyrin IX (PpIX). It emits a characteristic red fluorescence after excitation by a specific blue light, generated by a xenon short arc lamp (D-Light) [16]. The basis for the preferential uptake of ALA by PGs relative to surrounding tissues remains unclear. ALA's use has been described as "optical biopsies" in parathyroid surgery, but has not been shown to shorten intraoperative times. Like MB, ALA has its limitations. For example, due to the shallow penetration of the stimulating light, the PGs have to be largely dissected to allow detection. Furthermore, there is the possibility of a high degree of user error, as excessive photosensitization of the surrounding tissues can make PGs virtually indistinguishable. ALA administration can also cause transient elevations in liver enzymes, although no episodes of associated life-threatening liver failure have been described. Perhaps the biggest impediment to widespread adoption of ALA injection, however, is the inconvenience of shielding patients from light for 48 hours after surgery to prevent a potential phototoxic skin reaction.

ICG

The pairing of ICG with NIRI technology marked an important step in real-time identification and preservation of PGs during thyroidectomy. ICG is a water-soluble, anionic tricarbocyanine dye and serves as an intravascular contrast agent to assess perfusion [12]. The fluorescence spectrum of ICG is approximately 820–834 nm after injection [26]. ICG use with near-infrared fluorescence has established a role in other procedures such as intraoperative angiography, extrahepatic cholangiography, coronary artery bypass graft, lymph node mapping, and intestinal anastomosis [12, 27].

ICG demonstrates selective uptake in the PGs relative to surrounding tissues. This fact, coupled with a favorable safety profile, made ICG a feasible option to possibly assist with real-time intraoperative identification of PGs. The only adverse side effect of ICG is that it can cause urticarial and anaphylactic reactions in those with iodinated contrast allergies. It has a half-life of around 2.5–3 minutes.

However, while ICG utilization may facilitate PG detection, it can also be employed to assess vascular flow and viability of the PGs. This information can then be used to direct the critical decision of whether to excise and then reimplant a

compromised PG. This represents a major departure from traditional methods of assessing perfusion, such as observation of the color, ability to bleed, or temperature of the gland [24, 25]. In addition to its excellent safety profile, this ability to assess perfusion and viability of the PGs is one of the key differences between ICG and MB or ALA.

To employ the ICG-based approach, a light source and camera set to the appropriate wavelengths, at about 805 nm for absorption and a peak emission at 835 nm, are required. There are several imaging systems available for this technique, including Spy (Stryker), Fluobeam (Fluoptics), and the Firefly system (Intuitive Surgical) designed for robotic surgery. On these platforms, greater vascularization is represented by more intense color of the PGs.

Various groups have studied the utility and feasibility of ICG in both thyroid and parathyroid surgeries [17, 25, 28–30]. Zaidi et al. were one of the first to study the utility of ICG imaging during total thyroidectomy for malignant and nonmalignant cases [29]. Perfusion was classified by the degree of fluorescence into three categories, such that the lowest fluorescence intensity suggested poor perfusion: 3+ (>70% uptake), 2+ (30–70%), and 1+ (<30%). In this study, 85 PGs were identified visually. Seventy-one of the 85 (84%) showed ICG fluorescence. The false negative rate (when the lack of ICG fluorescence did not correlate with visual assessment of gland viability) was 6%. The pattern of ICG uptake correlated with postoperative serum parathyroid hormone (PTH) levels. One of the limitations of this study is that the glands that were identified visually and via ICG were not confirmed with frozen sections to determine a true false positive or negative rate. It also did not describe the rate of permanent hypocalcemia due to permanent hypoparathyroidism.

Fortuny et al. also studied PG detection and perfusion during total thyroidectomy [6]. They showed that after thyroidectomy the lack of a single, well-perfused PG, determined by ICG uptake, reliably predicted hypocalcemia. Of the 36 patients in the study, 30 had at least one well-vascularized PG at the end of surgery. Six patients did not have at least one well-perfused PG. Two of these six patients experienced transient hypoparathyroidism. None had permanent hypocalcemia. The PG perfusion status was assessed visually with a three-point grading scale similar to that use in the Zaidi study. If there was discordance between visual and ICG assessment of perfusion, the gland was incised to determine if there was any bleeding. If there were no signs of bleeding, the gland was excised and reimplanted.

The Triponez group, from Switzerland, subsequently conducted a randomized trial, with a much larger number of patients ($n = 196$), demonstrating that ICG was reliable in determining PG perfusion after thyroidectomy [5]. Of these patients, 146/196 had at least one well-perfused parathyroid gland seen with ICG imaging. These 146 patients were then randomized. The control group was supplemented with calcium and vitamin D, with postoperative labs (calcium and PTH levels) drawn on postoperative (POD) #1 and POD #10–15. The intervention group did not have labs drawn on POD #1, nor did they receive supplementation. They did have POD #10–15 labs drawn to confirm that PTH levels were normal. Of the randomized patients, there were no significant differences seen in the two groups in regard

to hypocalcemia or hypoparathyroidism. The authors concluded that patients with at least one well-perfused PG based on ICG imaging would not be hypoparathyroid postoperatively. Interestingly, of the 50 patients in whom no PGs were found to be well-perfused, 11 presented with hypoparathyroidism on POD #1 and 6 on POD #10. Similar results with ICG have been reported for video-assisted and robotic thyroidectomy [9, 31].

The use of ICG to detect diseased PGs, such as in primary hyperparathyroidism (HPT), has not been widely studied, but several groups have described some results. Berber and colleagues are among the few who describe their experience with ICG in the setting of surgical parathyroid disease [30]. In one study, 33 patients underwent parathyroidectomy, with 112 PGs identified visually; 20 patients had a single adenoma, 7 had double adenomas, and 6 had four-gland hyperplasia. 104/112 (92.9%) of these glands demonstrated ICG uptake. The authors reported that this shows that intraoperative ICG can aid in detection of PGs. The study also showed there was a significantly higher degree of fluorescence in patients with preoperative calcium levels of >11 mg/dl and with larger glands (>10 mm). Results regarding the degree of fluorescence of pathologic glands have been conflicting [32]. This represents one of the many questions regarding these emerging technologies that need further research investigation. One aspect of parathyroid surgery that does seem to benefit from ICG evaluation is in assessing perfusion of the remnant PG after 3.5 gland excision for four-gland hyperplasia [12, 30, 33].

DeLong et al. are another group that has examined the use of ICG to identify PGs in the setting of primary HPT [34]. Of the 55 patients who underwent preoperative localization with sestamibi scan, 18 patients failed to localize. At surgery, all 18 of these patients were found to have a single adenoma as the cause of their disease. These all fluoresced with ICG. Glands that were not identified with other imaging modalities also were seen with ICG during surgery. This study highlights that ICG may have a potential use in identifying PG adenomas that were non-localizing with preoperative imaging modalities.

Autofluorescence Imaging

While ICG clearly aids with assessing the vascularity of PGs, its ability to facilitate the detection of PGs is still unclear. More recently, AF of PGs without enhancement of ICG (or other agent) has become an area of significant research interest [35–37]. This concept is distinct from other techniques (such as injection with ICG) in that PGs have an endogenous fluorophore that emits NIR light at a peak emission wavelength of 820 nm when illuminated with light at 785 nm [12, 24, 38]. Therefore, no adjuvant agent is used to induce fluorescence. The mechanism of AF of PGs is still unclear, but there are several studies that suggest the calcium-sensing receptor protein (CSRP) as a potential fluorophore candidate [12, 36]. This theory is based on the fact that the CSRP has its highest concentration in PGs compared to the thyroid gland and other tissues.

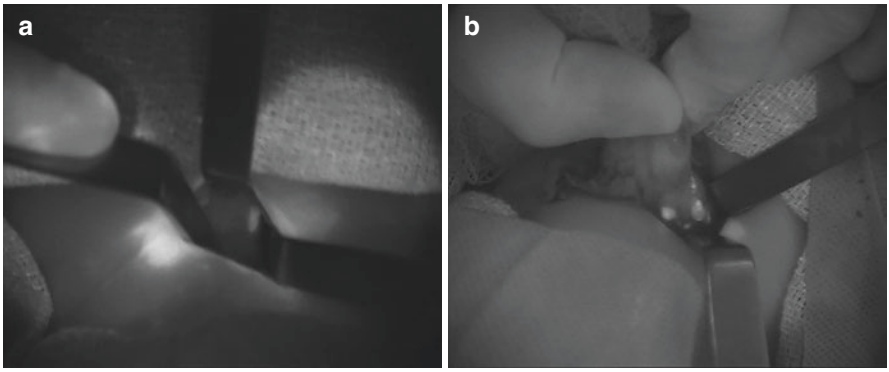

Fig. 15.1 (**a**) A camera-based system used to perform near-infrared imaging with endogenous parathyroid gland autofluorescence demonstrates the view obtained of a parathyroid gland during thyroid surgery. (**b**) After the thyroid is delivered through the wound, two parathyroid glands can now be seen

One of the major problems with using ICG-based imaging is that with injection everything in the field tends to fluoresce, because of their inherent vascularity. Thus, differentiating the PGs from the thyroid gland, for example, can be quite challenging, even for experienced surgeons. AF-based identification largely avoids this issue as the degree of AF of the PGs is conspicuously greater than the surrounding tissues. Thus, the likelihood of being able to distinguish PGs from other structures is greater compared with ICG imaging.

For AF examination of the PGs, some of the same devices employed for ICG assessment can be used (Fig. 15.1a and b). In addition to these camera-based systems, a probe-based option is available. This device, PTeye (Medtronic), houses both the stimulator and receiver in a low-profile probe. When this probe is applied to tissue, the accompanying monitor shows its absolute degree of fluorescence and a ratio compared with the measured thyroid fluorescence. A ratio above a certain amount indicates that the contacted tissue is likely parathyroid (Fig. 15.2a and b).

Critically, AF can only aid in detection of PGs. De Leeuw et al. showed that AF remains stable even 1 hour after resection of PGs or when fixed in formalin; therefore, AF is not related to perfusion [1]. This AF characteristic of PGs can be used for the benefit of identification. However, ICG injection is still needed if knowledge of perfusion and gland viability is desired.

A team of researchers at Vanderbilt University, led by Dr. Anita Mahadevan-Jansen, has performed much of the seminal work in the area of PG AF. In 2013, they demonstrated the efficacy of using intraoperative NIR cameras to detect PGS during thyroid and parathyroid surgeries [35]. The identification rate with AF was 100% among the 45 patients undergoing surgery.

This same group then published a study that examined various factors effecting fluorescence intensity of PGs [36]. They found that BMI, disease state, vitamin D level, and calcium levels accounted for the variability in intensity signal. Age, sex,

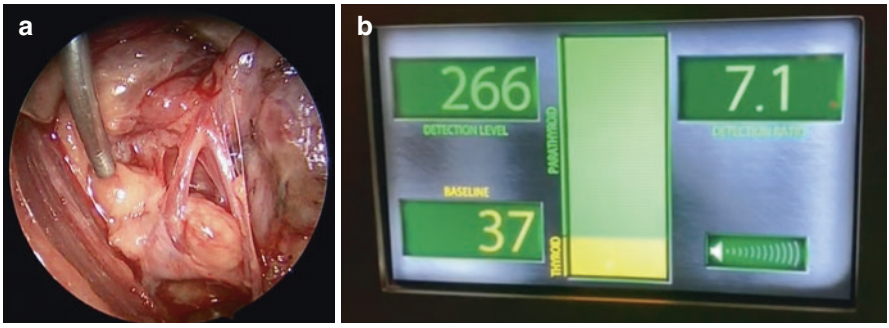

Fig. 15.2 (**a**) A right-sided, superior parathyroid gland is stimulated by the near-infrared imaging probe. (**b**) The console of the PTeye shows the absolute degree of fluorescence (on the left) and the ratio compared with the measured thyroid fluorescence (on the right). The high ratio confirms the contacted tissue is parathyroid

ethnicity, and PTH levels had no apparent influence. It is somewhat intuitive that a high BMI might cause lower intensities as adipose tissue could limit the depth of penetration of the stimulating light. The explanation for why high calcium levels and low vitamin D levels also resulted in lower PG intensities is less clear. It may be that the high calcium levels in primary HPT may suppress the function of the CSRP. Interestingly, they discovered that the detection rate of PGs was lower in renal-related secondary HPT. Only a 54% detection rate was achieved in this group, compared to 99% for other disease states, including thyroid malignancies, nonmalignant thyroid pathologies, primary HPT, and tertiary HPT. While the explanation for this finding is still unclear, it is possibly due to a downregulation of the CSRP in secondary HPT.

Kahramangil et al. looked at PG detection with AF in the first ever multi-institution study [38]. They reported that AF facilitated identification of PGs, as 37–67% of PGs were detected with AF before being recognized by the surgeon in the conventional manner. Although there was variability in this rate between centers, there was a concordance in detecting AF from 97% to 99% of the PGs.

One important question that is just beginning to be answered is how pathologic parathyroid states impact AF qualities. Kose et al. delved into this question using the Fluoptics device [39]. They attempted to determine if AF intensity and patterns differed for different parathyroid pathologies. In this study, 50 patients underwent bilateral neck exploration. In this study, 199 PGs were identified and 96% (n = 192) exhibited AF greater than background tissues. Fifty-two PGs (26%) were found by AF prior to visual identification. Hyperfunctional PGs exhibited a lower mean normalized AF intensity compared with normofunctioning glands. Additionally, they demonstrated a more heterogeneous pattern of fluorescence. While these results conflict with some other studies, the impression that hyperfunctional PGs demonstrate lower fluorescent intensity has also been reported by others [37, 40].

The Future of Fluorescence Imaging

Fluorescence imaging, with or without ICG, appears to be a promising method for identification and/or assessment of PGs. However, as the inconsistent results of studies with these modalities reveal, our understanding of their precise technique for use, interpretation, and value is quite limited at this point.

In addition, the challenges related to PGs in thyroid and parathyroid surgery are vastly different. In thyroid surgery, for example, while identification of the PGs is important, perhaps more crucial is the ability to assess their viability. This contrasts with parathyroid surgery, where recognition of the PGs (and the ability to differentiate normal from pathologic glands) is most important. As a result, in parathyroidectomy, the use of ICG is likely to be less relevant. In thyroid surgery, however, it may be that the optimal approach will be to utilize both methods, with AF used initially to aid in detection followed by ICG injection to appraise the vasculature.

It is also unclear in which types of cases should fluorescence imaging be utilized. Does it provide enough benefit to be employed in any routine total or completion thyroidectomy? Perhaps it is only in select scenarios, such as revision surgeries, where its use will be warranted. Similar questions exist regarding which type of surgeon will gain the most from these technologies. Is it highly experienced surgeons, performing the most complex cases, who will most benefit or is it less experienced, lower volume surgeons who need the most support in recognizing and preserving PGs?

The types of questions surrounding fluorescence imaging of PGs are similar to those that arise with any emerging technology or surgical technique. In that regard, fluorescence imaging is similar to intraoperative recurrent laryngeal nerve monitoring when it was first introduced. Many questions about neuromonitoring's optimal use and role were raised, and only with extensive research have many of these questions been answered. With the benefits now defined, neuromonitoring has now been widely adopted in thyroid surgery. Given the potential benefits offered by PG fluorescence imaging, with additional study, this technology is also likely to become a routine part of thyroid and parathyroid surgery in the future.

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Chapter 16
Intraoperative PTH Monitoring

Ahmad M. Eltelety and David J. Terris

Historical Perspective

Parathyroid hormone (PTH) was first isolated in a stable form using phenol extracts at room temperature by Aurbach in Massachusetts in 1959 [1]. With the application of considerable additional technology, the process evolved over 30 years culminating with the first use of rapid intraoperative parathyroid hormone (ioPTH) monitoring in 1988 by Nussbaum and his team [2] to confirm satisfactory removal of all hyperfunctional parathyroid tissue before leaving the operating room. Despite using ioPTH monitoring, these pioneers still undertook bilateral neck exploration [2]. Irvin and colleagues [3, 4] in Miami took the next step in the early 1990s by performing focused parathyroidectomy guided by preoperative imaging localization studies and with confirmation of intraoperative cure using the rapid assay. He is therefore credited with popularizing this practice in the United States (Fig. 16.1).

In the mid-1990s, the first assay designed specifically for intraoperative application – the Quick-Intraoperative Intact PTH assay – was introduced by Nichols Institute Diagnostics (San Clemente, California) [4]. System instrumentation included a microcentrifuge, heater-shaker apparatus, bead washer, and single-well luminometer. Modules were installed on a mobile cart that could be housed in the operating room or close to it. This system had an incubation time of 7 minutes giving a net turnover time of 12–15 minutes.

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M. C. Singer, D. J. Terris (eds.), *Innovations in Modern Endocrine Surgery*,
https://doi.org/10.1007/978-3-030-73951-5_16

Fig. 16.1 George Irvin is credited with introducing rapid intraoperative parathyroid hormone testing into clinical practice, and therefore spawning the era of the focused or minimally invasive parathyroidectomy

Eventually, automated rapid ioPTH assays were introduced. These had the advantages of less frequent need for calibration and reduced hands-on time for the technologist. The drawback of these systems was that they required a fixed location in the operating room or a satellite laboratory or, more often, were located in a central laboratory which added to the turnaround time. Additionally, the automated assays had to be singularly devoted to ioPTH testing because of the calibration needed. The first automated assay was the Turbo Intact PTH assay from Diagnostic Products Corporation (Los Angeles, California). The assay has an incubation period of 10 minutes with a total assay time of approximately 18 minutes.

Despite inherent logistical challenges, central laboratory platforms utilizing these standard PTH assays are rapid enough to allow for intraoperative use [4]. These became the standard when the FDA removed the Nichols Diagnostics assay from the market, forcing surgeons to utilize these more time-consuming and less convenient laboratory-based assays. In 2006, Future Diagnostics (Nieuweweg, the Netherlands) introduced a new point-of-care system [5] which achieves turnaround times similar to the original Nichols system (7–8 minutes).

The interpretation of the assay findings has also undergone a gradual transformation, with increasingly rigid criteria leading to a lower risk of failure in patients with double adenomas. This important principle will be addressed in greater detail later in this chapter.

Technical Considerations

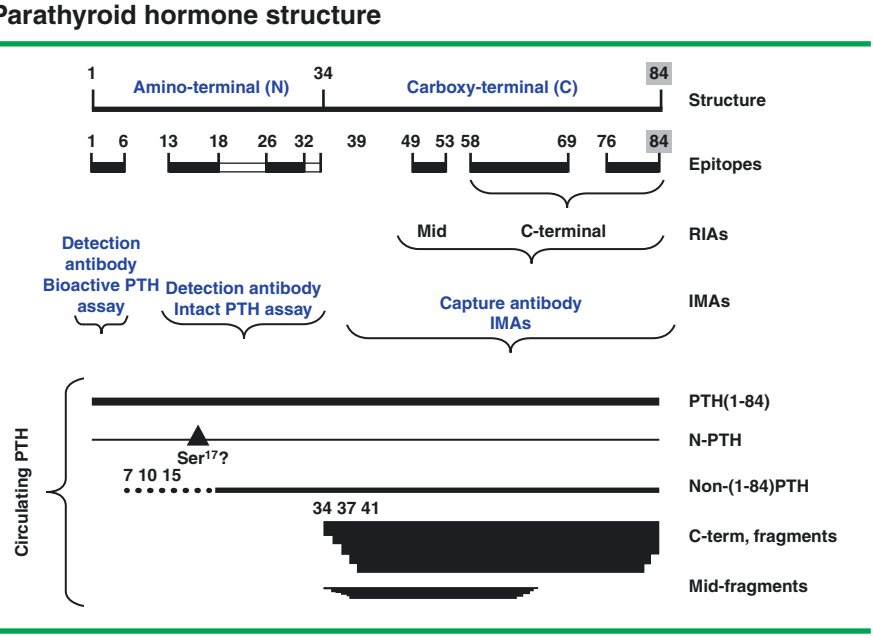
Assay Characteristics

The PTH molecule is exclusively produced by the parathyroid glands. The full-length molecule consists of 84 amino acid residues, and has a carboxy terminal and

an amino terminal. The hormone is secreted in a pulsatile manner with minute-to-minute and circadian variability [6, 7]. The half-life of the intact PTH molecule is short and ranges between 2 and 7 minutes, but with considerable interindividual variation. The intact circulating molecule undergoes initial hepatic cleavage yielding an inactive carboxy-terminal fragment which later is subject to renal excretion. This fragment has a longer half-life than the intact (1–84) PTH molecule itself [8, 9].

A radioimmunoassay (RIA) was used first to measure the PTH level. The sensitivity of this assay was low as it measured biologically inactive fragments of the PTH molecule by virtue of the use of polyclonal antibodies to the carboxy terminals of the PTH molecule. Therefore, these assays were relatively inaccurate, especially in patients with renal hyperparathyroidism who had high levels of the biologically inactive carboxy-terminal fragments. An amino-terminal PTH assay was later utilized, but this also had challenges related to sensitivity [10]. Modern assays measure the intact molecule (Fig. 16.2) and are therefore quite accurate and reliable.

The immunoradiometric assay (IRMA) largely replaced the RIA for the measurement of serum (1–84) PTH levels. IRMA is a sandwich assay utilizing two



Schematic presentation of PTH(1-84) and the approximate location of the peptide regions recognized by the antibodies used in displacement-type RIAs and in "two-site" IMAs.

IMA: immunometric assay; PTH: parathyroid hormone; RIA: radioimmunoassay.

Fig. 16.2 The structure of the parathyroid hormone molecule is depicted. Early generations of the parathyroid hormone assay that were specific for the carboxy or amino terminal of the molecule were not as accurate as current assays which measure the intact molecule. (Reused with permission © 2019 Oxford University Press [39]

separate antibodies. The IRMA was eventually replaced by the immunochemiluminometric assay (ICMA), a third-generation PTH assay that has a similar mechanism of reaction as the IRMA, but utilizes a chemiluminescent binder rather than a radioisotope. The reagent used by the ICMA has a much longer shelf life than those required for the IRMA and is easier to use. The incubation time was reduced to 7 minutes by increasing the incubation temperature from 37 °C to 45 ° C. These modifications have led to a results reporting time of approximately 7–8 minutes. The OR-based STAT intraoperative intact semiautomated chemiluminescence immunoassay (Future Diagnostics, Nieuweweg, the Netherlands) is now the most commonly used assay for point-of-care ioPTH monitoring (Fig. 16.3) [11, 12]. EDTA plasma is used for quantitative determination of the intact PTH levels.

Source of Blood Samples

Blood samples obtained for ioPTH monitoring may be either arterial or venous, peripheral or central, and obtained intermittently or from an indwelling catheter, each with its own advantages and drawbacks. An arterial line provides a reliable source for as many samples as needed; however, it has the disadvantage of being

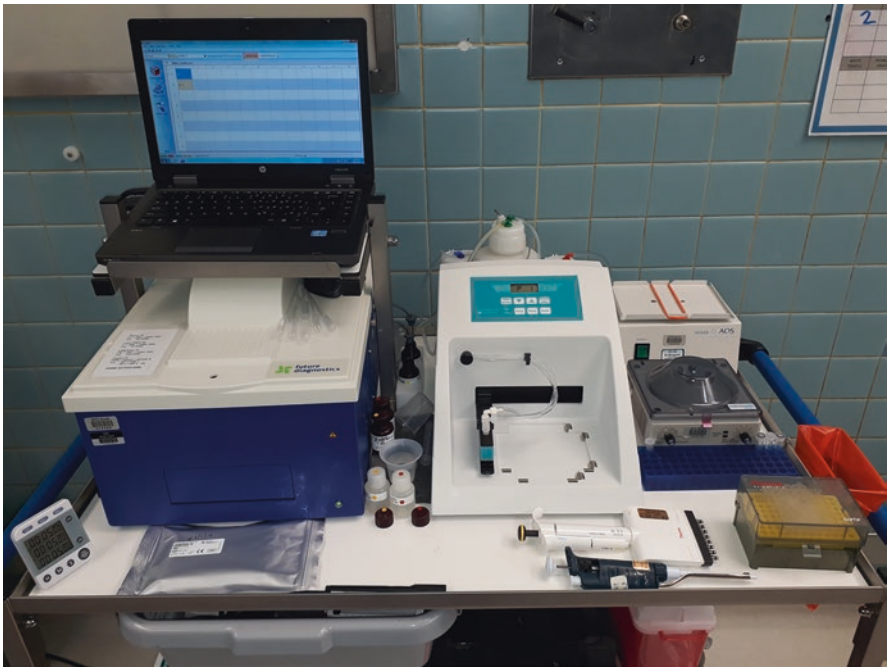


Fig. 16.3 The Future Diagnostics the point-of-care intraoperative parathyroid hormone assay which is a mobile system that is deployed to the appropriate operating room. The setup at our institution is demonstrated

an invasive procedure with the need for specific training and a small potential for complications [13]. More commonly, a venous source is chosen for sample collection. A central venous source may be used (internal jugular vein (IJV)), with the benefit of easy access in the surgical field. IJV sampling, however, incurs the remote risk of air embolism. To obviate this potential risk, peripheral venous access is typically preferred. While the antecubital fossa vein may be utilized, it is close to the surgical field which may result in interference while drawing the sample. Instead, we prefer foot veins as they are readily accessible, safe, and convenient for both the surgical and the anesthetic teams (Fig. 16.4), especially when the operating table has been rotated away from the anesthesiologist to provide improved access to the neck.

Modern Application

The ioPTH assay has emerged as an important tool for modern parathyroid surgery, particularly when limited exploration is undertaken. Critical elements related to the proper application of the assay include the timing of acquisition of levels and the interpretation of this data. The algorithms and criteria for surgical termination that were originally applied are now recognized to be somewhat simplistic, but a period of study and experience was required in order to refine our understanding. Some of the prevailing criteria and the subsequent evolution are detailed below.

Previously Proposed Algorithms for Intraoperative Application of the PTH Assay

Miami Criterion The first algorithm that was proposed for the interpretation of the results of ioPTH was the Miami criterion. Baseline levels were obtained prior to inci-

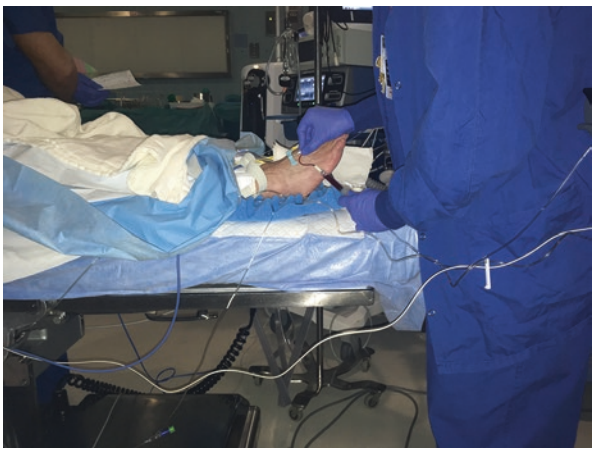


Fig. 16.4 While there are a number of access options for obtaining blood sample, the preference is to use a vein from the patient's foot which is particularly convenient since the operating table is rotated away from the anesthesiologist providing ready access

sion and just prior to interruption of the blood supply of the adenoma (so-called pre-incision and pre-excision levels), and then 10 minutes after removal of the hyperfunctional parathyroid tissue. Patients were considered to be biochemically cured if the ioPTH level dropped more than 50% from the highest of the two baseline measurements after excision of the clinically abnormal parathyroid tissue. The accuracy of this criterion was reported to be 97% for single-gland disease. The Miami group reported an incidence of multiple adenomas or four-gland hyperplasia of 4%. It was noted that the sensitivity and specificity of the Miami criterion are reduced when managing multiple-gland disease. For more than single-gland disease, the sensitivity was 90%, specificity was 94% and accuracy was 92% [3, 11, 14–16].

Rome Criterion Over time, surgeons appreciated the need for a stricter metric to determine biochemical cure. The Rome criterion therefore emerged, [17] in which patients were deemed cured when the ioPTH level achieved a greater than 50% drop to normal at 20 minutes and/or <7.5 ng/L lower than the 10-minute level [18].

Augusta Criterion A single-surgeon database was utilized to explore for a more flexible algorithm that contained a more stringent criterion to determine cure. Pre-excision levels yielded no value because of the recognition of the importance of achieving a normal level regardless of the proportional decline. The algorithm therefore endorses obtaining a pre-incisional baseline level and then post-excision levels at 5, 10, and 15 minutes after removal of clinically abnormal parathyroid glands. The procedure termination threshold was set as at least a 50% decline in the post-excision level *and* to within the normal reference laboratory values. Earlier termination of the procedure occurred if the 5-minute level met these criteria, resulting in a significant reduction in hospital costs [19]. The algorithm is depicted in the graphic in Fig. 16.5.

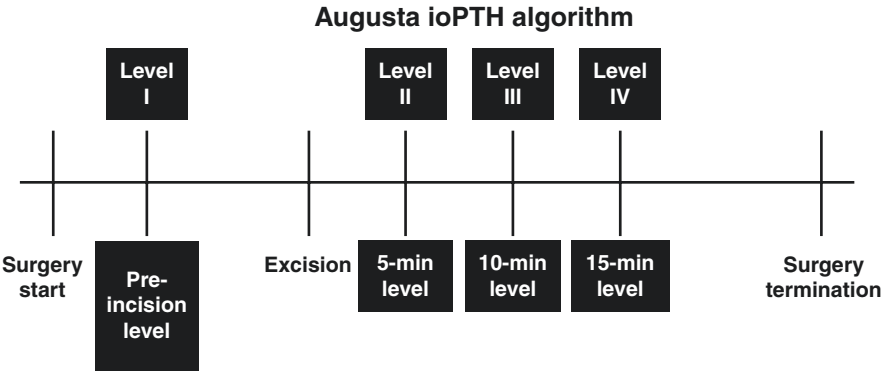


Fig. 16.5 A number of algorithms for obtaining and interpreting the intraoperative parathyroid hormone levels have been described. A flexible and predictive algorithm was described in Augusta, and allows for early assessment with a 5-minute post-excision level, but without wasting resources for a "pre-excision level," which never impacts the decision to terminate the operation

Modern ioPTH Interpretation

Over time, it has become clear to most high-volume surgeons that, despite a desire for a strict formulaic equation into which one can plug the ioPTH data to know when to stop an operation, this is not always clinically appropriate. Rather, to achieve optical outcomes, we need to let the numbers tell their story. Therefore, a state of dynamic interpretation should be exercised by the surgeon on an individualized basis to predict whether a patient is cured or not [20]. Factors that may influence this decision include patient age, comorbidities such as renal and hepatic disease which may cause slow PTH degradation, extent of dissection prior to gland excision, preoperative localization information, and the baseline PTH level. When bearing all of these factors in mind, an elderly patient with renal dysfunction, multiglandular disease, and extensive gland manipulation prior to excision can potentially be deemed to be cured at a PTH level higher than a healthy younger patient with a single abnormal gland, no associated comorbidities, and strongly localizing preoperative images.

Importantly, the ioPTH levels should never plateau during surgery at a level above 40, as this would predict the presence of additional hyperfunctional tissue. This was highlighted in a recent article [21] in which an absolute threshold of 40 was proposed as a meaningful metric for determining cure. Efforts to eliminate the need for baseline levels [22] have not been able to be substantiated, and may instead prolong the operative encounter [23].

Interpretation of ioPTH in Renal Patients

The use of rapid ioPTH monitoring during parathyroidectomy for renal hyperparathyroidism is less well-established. The principal value of the assay relates to the high prevalence of supernumerary parathyroid glands in this patient subset which is difficult to predict and discernible usually only with monitoring of the PTH level intraoperatively. This represents an important strategy for avoiding surgical failure caused by undetected hyperfunctional parathyroid tissue, which would be associated with the need for remedial surgical interventions [24–26].

There is not yet consensus regarding the values at which surgery for renal hyperparathyroidism should be terminated. In one report, the 20-minute post-excision level was a good predictor of the long-term PTH level in both dialysis-dependent and renal transplantation patients [24]. In another study conducted by Seehofer et al., the investigators revealed that 15-minute post-excision ioPTH values less than or equal to 150 pg/ml were good indicators of biochemical cure and surgical success (98.7% of patients with renal failure) [27]. One report indicated that a 60% decline from baseline of the ioPTH level at 10 minutes after excision of the final abnormal gland is sufficient to conclude surgery, predict cure, and stop further exploration [28]. Hiramitsu and his team reported that a 70% drop in the ioPTH level was

necessary to consider surgery successful [29]. Ohe et al. concluded that an 80% decline at 20 minutes was needed to predict cure [30]. Finally, Weber et al. described a requirement for a decline of at least 90% in the ioPTH level to achieve a 97% cure rate in patients with renal hyperparathyroidism [31]. Clearly, further study is needed to better define the anticipated degradation pattern of parathyroid hormone levels in this special population of patients, and therefore achieve a consensus around the optimal thresholds for termination of surgery.

Novel Uses

Because the capability for rapid analysis of samples for parathyroid hormone level has become so accessible, additional uses for this technology have emerged. These adjunctive measures allow for identification of tissues and lateralization of the hyperfunctional parathyroid glands, either preoperatively or intraoperatively.

Tissue Aspirates: Preoperative and Intraoperative

A rapid parathyroid assay can be used to differentiate between parathyroid and non-parathyroid tissues using the washout from a needle aspirate [5]. This has been described and practiced for several years and is typically reserved for the re-operative patient. A 25-guage needle attached to a 3-ml syringe is used to aspirate the excised tissue with multiple passes. The aspirate is then diluted in a 3-ml normal saline. This fluid is then analyzed for PTH using a point-of-care assay system. Values equal to or less than the baseline serum PTH level were used to identify non-parathyroid tissue, while values at least twice the serum PTH level were diagnostic of a parathyroid tissue. Values between the previous two levels were considered equivocal. Frozen section analysis was conducted in the same time.

The information derived from this procedure can confirm the identity of suspected adenomatous parathyroid tissue prior to a surgical intervention and is especially helpful in distinguishing it from a lymph node or thyroid tissue. Avoiding the need to widely dissect into a scarred field offers the potential to reduce the risk of recurrent laryngeal nerve injury or inadvertent removal of normal parathyroid glands. Although there should be no hesitation in recommending this interrogation when facing the prospect of a re-operative surgery, there is peril in making this a routine approach [32], and the benefits therefore probably don't justify the risks.

The value of applying this strategy intraoperatively stems from the short results reporting time of as little as 7–8 minutes. When seeking to characterize indeterminate tissue intraoperatively, it is common to seek intraoperative consultation and frozen section analysis. The time needed to undertake intraoperative tissue analysis using a rapid ioPTH assay (after similarly aspirating tissue in situ or after excision) is considerably less than that required for frozen section. In one study, the difference

was 7 minutes, although a greater differential can be anticipated in most practice environments. At the authors' institution, the global cost of operative time was estimated to be $94 per minute; the frozen section analysis was estimated to cost $573. The cost of obtaining a single ioPTH level using the Future Diagnostics kit was $37.50, therefore resulting in a potential savings of at least $1193.50. The needle aspirate PTH level had a 100% sensitivity and specificity and was able to correctly classify sampled tissues as parathyroid or non-parathyroid in all patients [5].

Bilateral IJ Sampling

The ioPTH can play an important adjunctive role during surgery when lateralization of a hyperfunctional parathyroid gland is needed. Similarly to tissue aspirate assessment, this may be done prior to an anticipated surgery (so-called poor man's selective venous sampling) or more commonly intraoperatively, especially when a second adenoma proves difficult to find, and there is an unidentified gland on both sides of the neck. A jugular venous sample is obtained as low in the neck as feasible on both sides (Fig. 16.6) and sent for parathyroid hormone assay assessment to detect a differential between the sides.

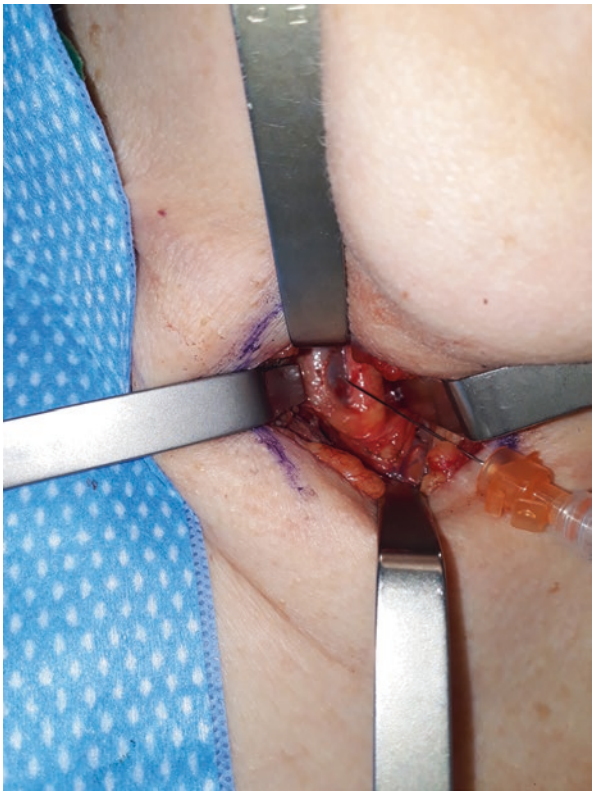


Fig. 16.6 Acquisition of a jugular vein sample is done quite easily as the carotid sheath is adjacent to the thyroid compartment. This is occasionally done when peripheral access is limited, but more commonly accomplished bilaterally in order to lateralize the hyperfunctional parathyroid tissue

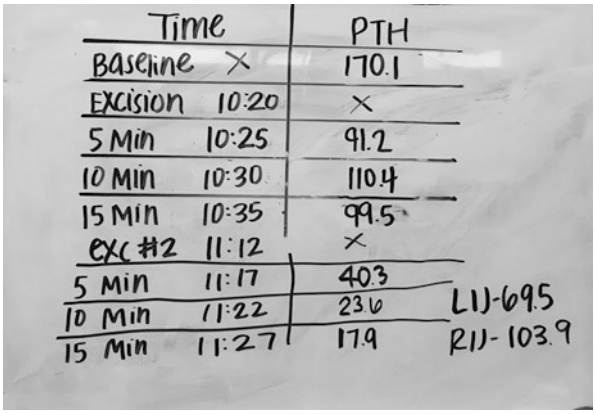


Fig. 16.7 This intraoperative parathyroid hormone assay data that is captured on a whiteboard in the operating room provides an excellent example of the value of monitoring for recognition of a double adenoma, and furthermore the capacity to lateralize the second adenoma. After removal of the index adenoma, the levels drop indicating that hyperfunctional parathyroid tissue has been removed. However, the plateau provides evidence that the patient harbors additional hyperfunctional tissue. The differential of the right internal jugular venous level of zz compared to the left IJV level of xx points to a right-sided adenoma. It is removed and the levels normalize

A difference of only 10% between sides in the preoperative setting has proven to be predictive of the side on which the hyperfunctional gland may be anticipated [33]. Intraoperatively, a 5% difference appears sufficient to guide the surgeon at least to the side of the missing abnormal gland [34]. Again, this strategy is not usually necessary except in the re-operative setting, or intraoperatively when the preoperative localization studies have been misleading or when a second adenoma proves difficult to identify. An example of a case where this proved helpful is demonstrated by the real-time results captured on a whiteboard in the operating room (Fig. 16.7), and reflects that after an adenoma is removed, the levels fall, but do not normalize; a bilateral jugular venous sample is considerably higher from the contralateral neck, and guided the dissection to the appropriate side, and the second adenoma. This case demonstrates both the critical importance of the ioPTH monitoring in the recognition of a double adenoma and the additional assistance in localizing the hyperfunctional gland.

Final Considerations and Future Possibilities

Changing Phenotype

The disease phenotype for the typical patient with primary hyperparathyroidism has evolved significantly with advances in biochemical testing, the use of autoanalyzers, and the practice of including calcium levels with the basic metabolic panel

assessed routinely by primary care physicians. Therefore, rather than manifesting with the classical symptoms of diseased bones, kidney stones, abdominal groans, and psychic moans, patients are much more likely to be asymptomatic (as defined by the several NIH consensus panels) [35]. Nonspecific neurocognitive symptoms, such as easy fatigability, poor concentration, mood changes, memory loss, and others, are often still present. The contribution of hyperparathyroidism in causing these nonspecific symptoms and therefore the role of parathyroidectomy in helping to improve such manifestations remain a matter of controversy and debate.

As the disease characteristics have changed due to earlier diagnosis, however, the indications for surgery, especially for patients with normocalcemic hyperparathyroidism, have also evolved. For patients with asymptomatic primary hyperparathyroidism, successful parathyroidectomy provides long-term stability and increase in bone mineral density [36, 37]. Patients with normocalcemia or normohormonal hyperparathyroidism pose a particular challenge for the surgeon insofar as properly applying the ioPTH assay in this population of patients with milder disease, and often a normal baseline PTH level. The 50% decline in the level is generally considered adequate to confirm a biochemical cure, although the reality is that the threshold for a bilateral four-gland exploration is going to be low in these patients because of the higher likelihood of multi-gland disease.

Faster Alternatives to the Rapid ioPTH

Considerable effort continues to be devoted to confirming parathyroid tissue intraoperatively and to more rapid assessment of PTH levels. There are now two FDA-approved autofluorescence devices for distinguishing parathyroid tissue from other tissues in the thyroid compartment (the Fluobeam 800 Clinic Imaging Device and the Parathyroid Detection PTeye System). The research aimed at a faster PTH assessment has been slower to reach fruition, but promising work so far has suggested that a rapid analyzer (as fast as 60 seconds) may be possible in the future [38].

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Part IV
Surgical Techniques

Chapter 17
Minimally Invasive Video-Assisted Parathyroidectomy (MIVAP) and Minimally Invasive Video-Assisted Thyroidectomy (MIVAT)

Paolo Miccoli and Michele N. Minuto

Minimally Invasive Video-Assisted Parathyroidectomy (MIVAP)

Introduction

In the 1990s the approach to surgery for primary hyperparathyroidism changed dramatically, as a result of progress in two main domains: the technical improvements in diagnostic tools such as ultrasonography and nuclear medicine techniques and the intraoperative monitoring of parathyroid hormone (PTH) with the rapid, intraoperative PTH assay.

Having preoperatively identified a likely single gland responsible for the disease, the surgeon was now longer compelled to perform a bilateral exploration of all parathyroid glands to decide which one should be removed. Rather, dissection could be limited to the single gland, immediately checking the impact of surgery on the disease. This allowed surgeons to "tailor" the extent of the dissection based on the preoperative and intraoperative results, thus limiting, in the majority of cases, the necessity of an extensive surgery with its related consequences.

At the same time, there was a diffusion of minimally invasive surgery procedures in many fields, often driven by the introduction of endoscopic techniques. These two trends allowed surgeons to envision new surgical solutions to remove parathyroid glands that, in the majority of cases, are very limited in size.

The first published attempt to use an endoscope in parathyroid surgery was described by Michel Gagner who, in 1996, reported a totally endoscopic technique aimed at the removal of a single parathyroid gland [1]. Even though the idea was

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M. C. Singer, D. J. Terris (eds.), *Innovations in Modern Endocrine Surgery*,
https://doi.org/10.1007/978-3-030-73951-5_17

appealing, the technique revealed two major flaws: the first was the challenge of ergonomics when using in a limited space surgical instruments that were designed for laparoscopy. The second flaw in this technique was the side effects of CO2 insufflation in an anatomical region that is not separated from the chest by any anatomical barrier [2]. Largely due to these challenges, the technique was soon abandoned.

In the second half of the decade, endocrine surgeons adapted surgical instruments specifically to be used in the neck region, trying to improve the ergonomics of the surgery. In Pisa, a new technique for parathyroid surgery, the minimally invasive video-assisted parathyroidectomy (MIVAP), was envisioned and performed. Due to its success, it was adopted all around the globe, becoming the most widespread endoscopic parathyroidectomy technique [3–5]. MIVAP relied on new instruments aimed at performing blunt dissection in the neck and specifically forged for this procedure. The endoscope used was adopted from the urologists' equipment (a 30° 5–7 mm endoscope routinely used for cystoscopy). This allowed a significant magnification (20×) of the small anatomical structures of the neck. Finally, the surgical space was maintained by using external retraction. This eliminated the need for CO2 insufflation, thereby removing the risk of hypercapnia. MIVAP was first described in 1997 in a series of six patients [6]. It was then modified slightly and validated in prospective studies in 1998 [7, 8].

The Technique

The MIVAP technique relies, as already specified, on external retraction created by two retractors placed at both ends of the 2 cm surgical incision. The incision is located on the line of the conventional Kocher's incision, to allow a proper and cosmetically valid conversion to traditional surgery, if needed. The incision is placed centrally in the neck, to allow a proper bilateral exploration of the parathyroid glands, when necessary [8, 9].

After having entered one side of the neck by means of blunt dissection aimed at exposing the thyroid lobe, the surgical field is created by retracting the thyroid lobe on one side and the carotid sheath on the other. The endoscope is then introduced together with the spatulas used for the dissection. At this point, the exploration is performed under endoscopic vision, including identifying and exposing the recurrent laryngeal nerve (intraoperative nerve monitoring can be employed if desired) and recognizing the pathologic parathyroid gland. Once the gland is identified, it can be dissected from surrounding structures by means of delicate blunt dissection performed with the two spatulas (Fig. 17.1). During the dissection, the vascular pedicle of the parathyroid gland can be visualized and clipped and the gland then delicately removed through the incision. After the parathyroidectomy, intraoperative PTH levels can be used to confirm that the patient is cured.

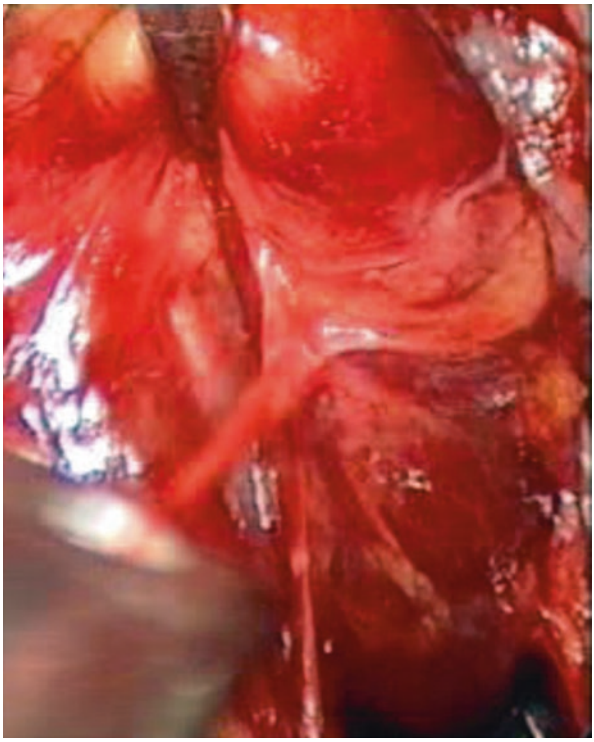

Fig. 17.1 The parathyroid has been identified and bluntly dissected by means of the two spatulas (in the picture, the small forceps are grabbing the hilum of the gland) that allow a delicate handling of the gland

Indications for MIVAP

Indications to perform MIVAP in a patient with primary hyperparathyroidism can (and should) be modified according to the experience of the surgeon. At the beginning of one's experience, the surgeon should choose patients with well-identified parathyroid adenomas, limited in size (less than 2 cm), no suspicion of multiglandular disease, and no concomitant thyroid disease (neither nodular disease nor thyroiditis). After a proper level of capability with MIVAP is acquired, the indications can be extended to all those cases that might require a bilateral parathyroid exploration.

Advantages and Key Points of the Technique

Among other advantages of MIVAP, the endoscopic view it provides represents a significant and essential tool, especially when dealing with a limited and narrow anatomical region such as the neck and exploring for glands that are often limited in size. The use of the endoscope is also cited as essential in the definition of "minimally invasive surgery" given by JF Henry, together with an incision that should not exceed 3 cm [10].

Similar to other minimally invasive parathyroidectomy techniques, the extremely limited surgical dissection reduces the risk of morbidity to a minimum. Injury to the recurrent laryngeal nerves is reported to occur in well under 1% of cases [11]. Due to the limited number of glands dissected, the risk of hypoparathyroidism is minimal.

Finally, from a cosmetic point of view, MIVAP produces an excellent aesthetic result, due to its limited size. A high degree of patient satisfaction with the cosmetic outcome of MIVAP has been documented [12].

Limits and Drawbacks

The primary limitation of MIVAP is the significant learning curve associated with it. Standard parathyroid surgery can be challenging, and excellent outcomes require a high level of experience. MIVAP is a technique that is even more refined and requires (like other endoscopic techniques) a significant learning curve of about 15–25 cases performed in a short period. The significant number of parathyroidectomies required to obtain a proper learning curve, together with the selection of patients who can undergo a MIVAP procedure, limits the number of surgeons who can master the technique.

Minimally Invasive Video-Assisted Thyroidectomy (MIVAT)

In 1999, after MIVAP was shown to be safe and beneficial, a similar technique designed for thyroid surgery was introduced. Minimally invasive video-assisted thyroidectomy (MIVAT) used the same access and approach to the thyroid gland as in MIVAP and was first trialed in patients with small thyroid nodules [13]. MIVAT gained broad acceptance as it offered several advantages with respect to other endoscopic thyroidectomy techniques:

- It is not purely endoscopic and is consequently closer to the technique of conventional thyroidectomy.
- It utilizes mostly reusable instruments, thus not raising significantly the costs of the procedure.
- Compared to remote access, endoscopic thyroidectomy procedures, MIVAT's direct access to the thyroid gland allows for a faster learning curve.
- Due to its simplicity and the significant reduction of surgical trauma caused by very limited dissection, it can be carried out on an outpatient basis.

The technique has now become one of the most widespread minimally invasive operations among thyroidectomies, including in the United States [14, 15]. While a popular technique, in endemic goiter countries, where the size of thyroid glands tends to be significantly larger, not more than 20% of patients can undergo MIVAT [16]. While initially described for benign thyroid disorders, MIVAT has been shown to be appropriate for thyroid carcinoma as well [17].

The Technique

In MIVAT, the approach to access the thyroid space is the same as used in MIVAP [16, 18]. The upper pedicle is ligated with any of the available advanced energy devices. Blunt dissection is then used to identify the critical structures, including the superior and recurrent laryngeal nerves (Figs. 17.2, 17.3, and 17.4) and both parathyroid glands. Once the lobe is completely freed, it is delivered through the incision, and the isthmus is divided in a downward direction taking care to expose the tracheal plane. The final step is to come through Berry's ligament. No drain is left in the neck, and the wound is closed with a few drops of sealant glue (Fig. 17.5).

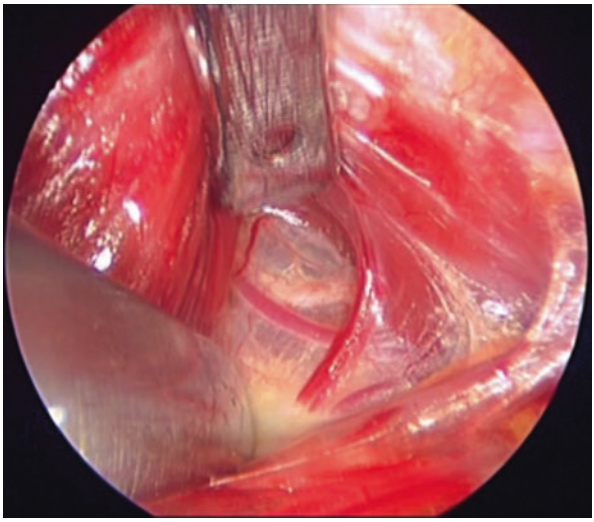

Fig. 17.2 The superior laryngeal nerve can be properly visualized with the endoscope, before dissecting the upper pedicle of the thyroid lobe. In this case, the right superior nerve can be seen between the two spatulas

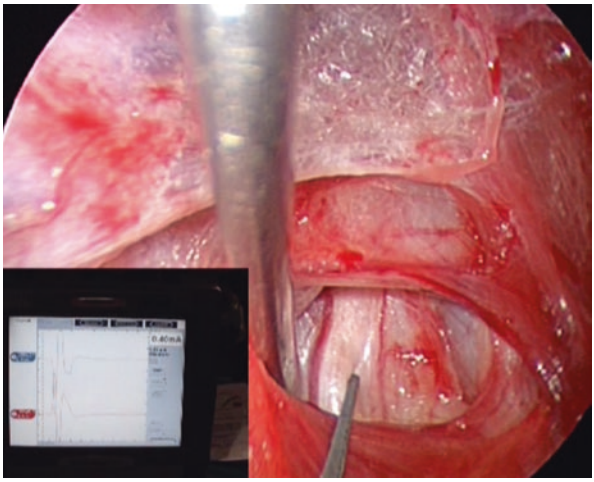

Fig. 17.3 The inferior laryngeal nerve on the right side has been exposed and can be tested with the intraoperative nerve monitoring system (small window on the right)

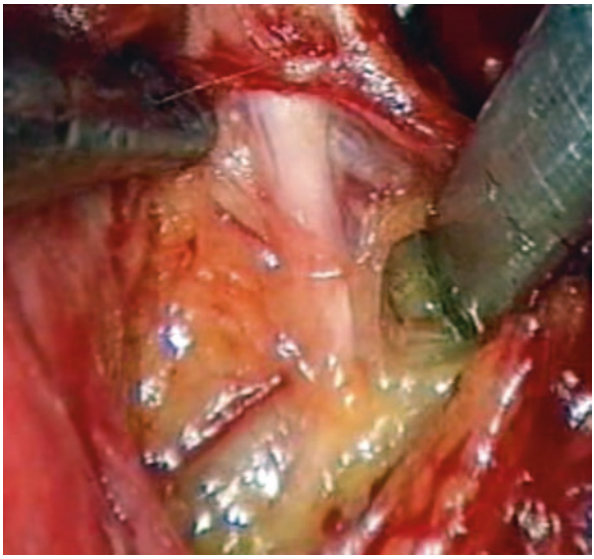

Fig. 17.4 The inferior laryngeal nerve on the left side has been exposed by means of a blunt dissection, performed with the two small spatulas

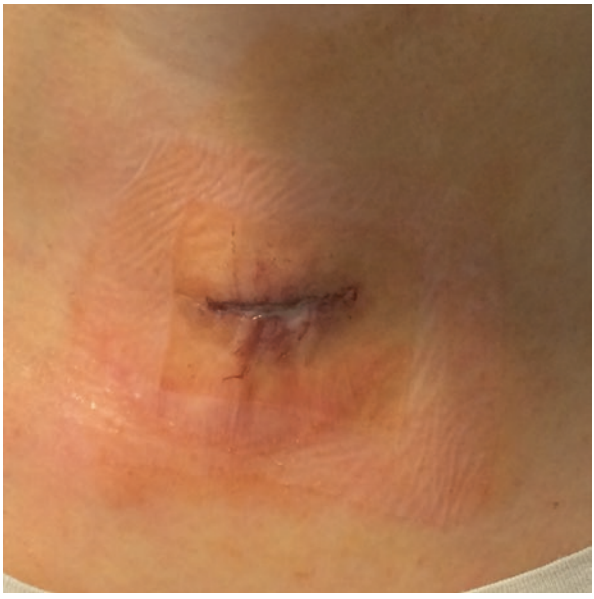

Fig. 17.5 The final cosmetic result: a 2 cm incision in the midline of the neck

Indications

MIVAT is not an operation appropriate for all thyroid surgery patients: its main limits are linked to the size of both the nodule and the gland. We generally assume that the thyroid gland should not exceed the volume of 25 ml, and nodules should not be larger than 3–3.5 cm in maximum diameter. Signs of severe thyroiditis, often

seen on preoperative ultrasound, should alert surgeons to the possibility of difficult dissection and should be considered a relative contraindication to performing MIVAT. While the indications for MIVAT are broad [19], a practice needs to perform a large number of thyroidectomies annually in order to maintain the appropriate skills required to perform it skillfully [20].

Once this technique was shown to be safe and feasible in benign pathologies, utilizing it for thyroid cancer was undertaken. Many surgeons expressed concern about this. However, MIVAT was shown to be an ideal operation for patients harboring low- or intermediate-risk, small carcinomas [17]. However, one needs to proceed with caution. From more than 20 years of experience, we learned that sometimes a posterior extracapsular infiltration of the primary tumor, mainly toward the tracheal plane, can escape even an accurate preoperative ultrasonographic examination. This extrathyroidal extension represents the major cause of conversion of MIVAT to traditional open surgery, even in very small, low-risk carcinomas. Additionally, a careful preoperative assessment for evidence of lymph node metastases, both in the central and the lateral neck, is needed. While central neck dissection can be performed with the aid of the endoscope, this is a technically challenging surgery.

Advantages of MIVAT

The most obvious benefit of MIVAT compared to traditional thyroidectomy techniques is the improved cosmetic outcome. MIVAT is traditionally performed through a 2 cm incision. This length is markedly shorter than that used in traditional thyroidectomy techniques.

In addition to cosmetic benefits, MIVAT offers patients improved postoperative courses. After MIVAT, patients' recoveries are both briefer and less painful compared to patients undergoing standard thyroid surgery. These MIVAT benefits have been shown consistently in several large literature reviews [21–23].

Conclusion

Both MIVAP and MIVAT were conceived to offer patients the benefits of a minimally invasive surgery while offering an optimal cosmetic outcome. The introduction of the endoscope into neck endocrine surgery was the key step that allowed these procedures to be developed. Both surgeries have been shown to be safe and appropriate for a broad range of patients. MIVAP and MIVAT continue to offer patients improved cosmesis and easier recoveries.

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Chapter 18
Robotic Transaxillary Thyroidectomy

Ehab S. Alameer, Grace S. Lee, and Emad Kandil

Introduction

The first endoscopic neck surgery was described by Gagner [1], who performed an endoscopic subtotal parathyroidectomy in 1996. This was shortly followed by an endoscopic right thyroid lobectomy by Hüscher in 1997 [2]. Minimally invasive video-assisted thyroidectomy (MIVAT), using a small cervical incision, was introduced by Miccoli in Italy in 1999 [3], and later modified and popularized in the United States by Terris [4, 5]. Since then, various types of endoscopic thyroid operations have been developed using axillary, breast, anterior chest, cervical, and, most recently, transoral approaches.

The endoscopic axillary thyroidectomy approach with CO2 insufflation was developed by Ikeda in 2000, using three axillary incisions to introduce laparoscopic instruments [6]. Endoscopic thyroidectomy faced several limitations: an unstable operative view, as the surgeon relies on an assistant to control the camera, difficulty in performing meticulous dissections around the recurrent laryngeal nerve and the ligament of Berry, limited access to the cervical space during lymph node dissection (due to straight endoscopic instrument design), and potential adverse physiologic changes such as hypercapnia or subcutaneous emphysema from CO2 insufflation [7–9].

In South Korea, WY Chung's group pioneered gasless, endoscopic thyroidectomy via the axillary approach, and later introduced the robot into the procedure in 2007 [10]. The utilization of the surgical robotic system significantly reduced

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M. C. Singer, D. J. Terris (eds.), *Innovations in Modern Endocrine Surgery*,
https://doi.org/10.1007/978-3-030-73951-5_18

mechanistic limitations of the endoscopic technique. The robotic platform provides the ability to control a high-definition camera system with a magnified, three-dimensional (3D) view as well as several multi-articulated, tremor-free instrument arms [11]. In 2009, the first case series of 100 patients who had undergone the gasless, robotic transaxillary thyroidectomy was published [12]. The technique has since undergone further modifications such as utilizing a single 6 cm axillary incision instead of making two incisions (an axillary incision and an additional anterior chest port). This less invasive modification has shown comparable technical, oncological, and surgical outcomes to the previous approach [13]. By 2017, more than 5000 cases had been performed by Chung's group alone.

When compared to the endoscopic transaxillary approach, the robotic transaxillary thyroidectomy was found to have a shorter total operative time (after accounting for robot docking time). The dissection time for the inferior pole and identification time for structures such as parathyroid glands and recurrent laryngeal nerve (RLN) were shortened, and more parathyroid glands were preserved with the robotic technique [14].

Over the past decade, many publications have supported the feasibility of robotic thyroidectomy in terms of safety, superior cosmetic results, and comparable oncologic outcomes [12, 15–17]. The success and popularity of robotic thyroidectomy is especially well established in Asia; however, dissemination of this technique in the United States has been rather slow and cautious [18]. Various factors have been implicated in the delayed adaptation of this technique in the United States and in Europe [19], including differences in cultural expectations, body habitus, high cost, and disease types [20]. The withdrawal of support for robot use in thyroidectomy by the US Food and Drug Administration in 2011 may have also played a role [11, 21].

A report of our experience with the first 100 cases of robotic transaxillary thyroidectomy was published in 2012 [22], demonstrating the feasibility of this technique for various indications including select cases of thyroid cancer and Graves' disease. Since then, several other reports and multicenter studies have proven the safety and feasibility of this approach in the United States [18, 23–28].

Patient Selection, Indications, and Contraindications

Careful patient selection is important in any surgery, but it is absolutely fundamental in ensuring successful robotic transaxillary thyroidectomy. Patient factors, tumor characteristics, and surgeon's operative experience should all weigh in when selecting an optimal surgical approach for each individual patient. Judicious patient selection is particularly critical for surgeons who are new to this technique, given the steep learning curve in mastering the technique.

Patients who are being considered for robotic transaxillary thyroidectomy should undergo the conventional preoperative workup. For patients with thyroid nodules, the assessment should proceed according to the American Thyroid Association's (ATA) Management Guidelines for Adult Patients with Thyroid Nodules [29]. Patients should meet the same indications for robotic thyroidectomy as for conventional thyroidectomy.

Table 18.1 Contraindications of robotic transaxillary thyroidectomy

Absolute contraindications	Relative contraindications
Large substernal or retropharyngeal goiters ≥ T3 thyroid cancer or any suspicious gross invasion Medullary thyroid cancer	Nodules greater than 5 cm Large goiters with substernal extension Known T2 well-differentiated thyroid cancer Graves' disease with substernal extension Obesity History of previous neck surgery or radiation

In 2016 the ATA published a consensus statement on patient selection and performance of remote-access thyroidectomy [28]. That statement suggests the following factors as being favorable for the performance of remote-access surgery: thin body habitus, the absence of excessive body fat along the flap trajectory, the presence of a well-circumscribed nodule, no larger than 3 cm, and a thyroid lobe smaller than 6 cm in largest dimension. The consensus group defined the ideal patient as a patient with <3 cm unilateral nodule who wishes to avoid a neck incision.

While these recommendations by the experts serve as general guidelines, it is important to note that patient selection criteria can be expanded as surgeons become more experienced with the technique. For instance, although the ideal patient has a body mass index (BMI) of less than 30 kg/m^2, we and others have demonstrated that robotic transaxillary thyroidectomy can be safely performed in patients with BMI over 40 kg/m^2 [22]. A large patient series at several high-volume centers also have shown that the technique can be safely performed in patients with Graves' disease, Hashimoto's thyroiditis, or thyroid cancer [22, 24, 30]. These were deemed relative contraindications in the past [30–35]. Like other remote-access thyroid surgery techniques, robotic transaxillary thyroidectomy is especially beneficial in patients with a history of keloid or hypertrophic scar formation. A summary of absolute and relative contraindications of robotic transaxillary thyroidectomy is shown in Table 18.1.

Surgical Technique

As with any novel surgical technique, this procedure has undergone several modifications since its inception. The overriding goal, when performing this technique, is not violating any of the core principles of safe and oncologically sound surgery.

The steps for routine robotic transaxillary thyroidectomy have been well described [10, 36, 37] (Figs. 18.1, 18.2, 18.3, and 18.4a and b). Several points warrant particular attention:

1. Proper positioning is crucial to avoid neurologic injury. The arm ipsilateral to the lesion (ipsilateral to the larger lobe of the thyroid in case of total or subtotal thyroidectomy) is positioned cephalad and flexed above the head (Fig. 18.1). This position optimizes exposure of the axilla and creates a short distance from the

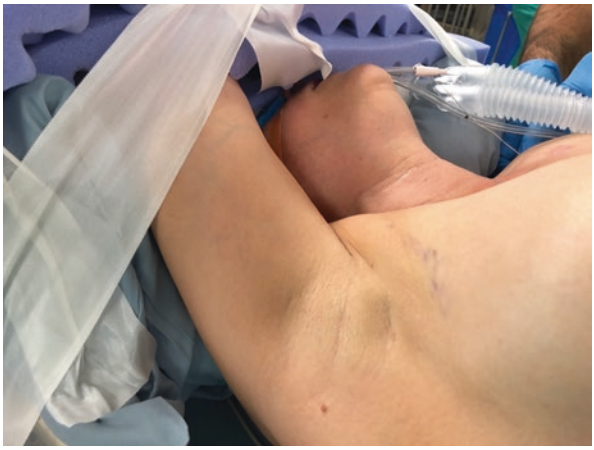

Fig. 18.1 Positioning of the ipsilateral arm for robotic transaxillary thyroid surgery

Fig. 18.2 SSEP is used to monitor the median and ulnar nerve signals prior to ipsilateral arm positioning

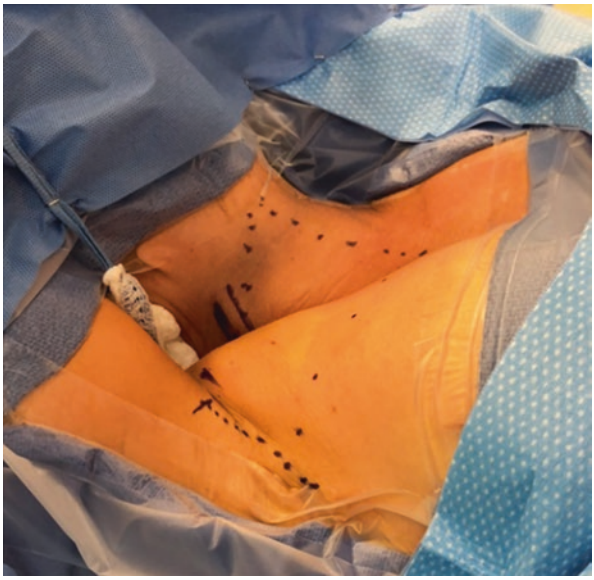

Fig. 18.3 Pre-incision markings for the transaxillary approach

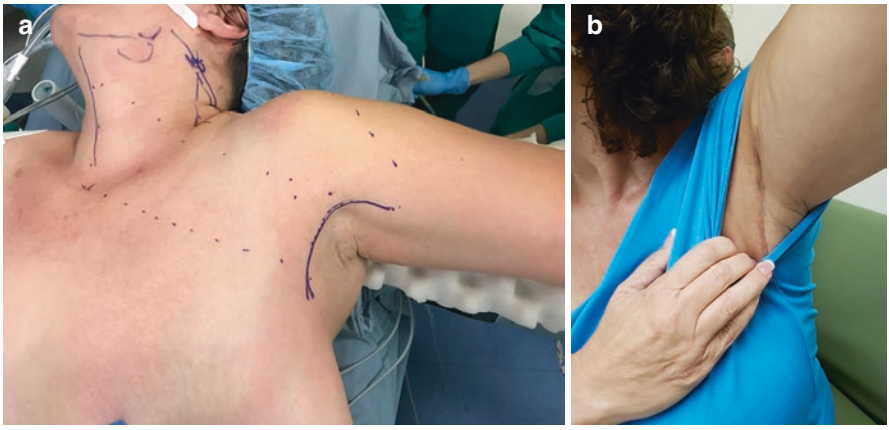

Fig. 18.4 (**a**) The level of the axillary incision and the extent of flap dissection are modified for lateral neck dissection. (**b**) A well-healed axillary incision following robotic transaxillary lateral neck dissection

axillary skin to the thyroid gland, which allows dissection. The contralateral arm is padded and tucked.

2. Somatosensory evoked potentials may be used to monitor the median and ulnar nerve signals [38] (Fig. 18.2).
3. As the thyroid is approached laterally, the exposure and subsequent dissection are easier if most of the gland is located anterior to the level of the internal jugular vein. We pay particular attention when performing dissection over the carotid

sheath, as some internal jugular veins can be markedly engorged and anteriorly located. In addition, the large caliber of the vein may potentially obstruct the view of the tracheoesophageal groove.

4. The level of the axillary incision and the extent of flap dissection can be modified if a lateral neck dissection needs to be performed (Fig. 18.4a and b).

Postoperative Care and Complications

Postoperative care after robotic transaxillary thyroidectomy is essentially the same as that for conventional thyroidectomy. Postoperative pain and nausea are usually minimal, comparable to open thyroidectomy. Most patients are discharged home on the same day. The surgical drain is usually removed at the first postoperative clinic visit, if the output from the drain is deemed appropriate.

Postoperative complications of robotic thyroidectomy have been evaluated by several meta-analyses, which include thousands of patients collectively [39–43]. No significant differences in terms of transient and permanent recurrent laryngeal nerve injury, permanent hypoparathyroidism, or hematoma formation were found between robotic and open thyroidectomy. There is a difference in incidence of transient hypoparathyroidism, which appears to be slightly higher in patients who undergo robotic thyroidectomy. Complication rates are lower in higher-volume centers [21].

Some observed complications are unique to this surgical approach. With robotic transaxillary thyroidectomy, brachial plexus neuropraxia is reported in about 0.2–2.2% of cases [19, 40]. This complication can be eliminated with the use of somatosensory evoked potential (SSEP) monitoring for the radial, ulnar, and median nerves [37]. A recent study at our institution evaluated a series of 137 robotic transaxillary surgeries performed on 123 patients using SSEP. Seven patients (5.1%) developed significant changes intraoperatively, but immediate arm repositioning resulted in prompt recovery of signals and complete return to baseline parameters with no postoperative positional brachial plexus injuries [38]. Rare cases of injury to the esophagus and trachea as well as mortality have been reported [21].

Advantages and Disadvantages

Many of the advantages of robotic transaxillary thyroidectomy result from use of the surgical robot system. Improved visualization has been described as a major benefit by most authors experienced in endoscopic surgery [9]. The three-dimensional, tenfold magnification view, and tremor-filtering system enable the surgeon to perform a more meticulous tissue dissection and significantly aid in handling of critical structures, including the parathyroid glands and the RLN. The operative view is the same, if not better than, in open surgery, as it allows the upper and lower poles of the thyroid to be easily visualized and manipulated. The multi-articulated,

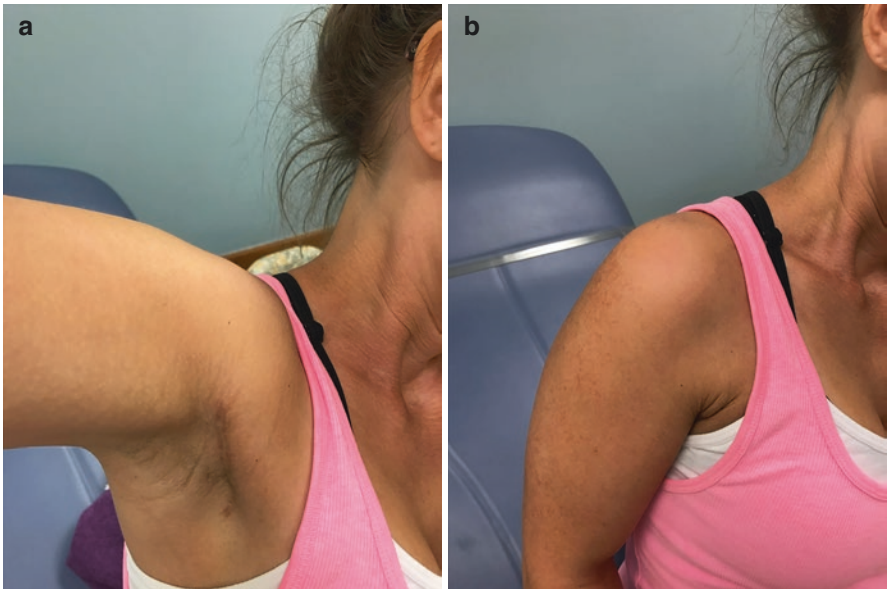

Fig. 18.5 (**a**) A well-healed axillary scar. (**b**) The scar is hidden in the natural arm position

wrist-free instruments of the robot provide easy access to the deep and narrow corner spaces and allow complete central node dissection [44, 45].

The gasless method utilized in the transaxillary approach avoids physiologic complications associated with CO_2 insufflation, namely, hypercapnia, respiratory acidosis, tachycardia, subcutaneous emphysema, and air embolism [46].

Another major benefit of this approach is the excellent cosmetic outcome, as the scar in the axilla is hidden when the arms are in their natural position (Fig. 18.5a and b) [44]. The superior cosmetic outcome has been validated in several studies [13, 40, 41, 43], and was shown to be associated with improved patient satisfaction and improved quality of life [32], when compared to the conventional thyroidectomy approach [9, 47].

Other advantages of robotic transaxillary thyroidectomy that have been reported include:

1. Absence of postoperative hypesthesia and fibrotic contracture in the anterior neck area, as no anterior neck flap dissection is performed [44]
2. Less intraoperative blood loss [39, 43]
3. Less postoperative swallowing difficulty [43]
4. The ability to perform total thyroidectomy with central and lateral neck dissections [45]

One of the main disadvantages of the transaxillary approach is the steep learning curve of 40–45 cases associated with it [22, 48]. Unfortunately, considerable difficulty exists in mastering the procedure even for surgeons who are experienced in conventional open thyroid surgery [45].

Table 18.2 Advantages and disadvantages of robotic transaxillary thyroidectomy

Advantages	Disadvantages
Advantages intrinsic to the surgical robot: Improved visualization Tremor filtering Multi-articulated instruments Gasless method avoids the risk of CO2 insufflation Excellent cosmetic outcome Adequate oncologic outcome Absence of postoperative hypesthesia and fibrotic contracture in the anterior neck Less sensory changes in the neck Less swallowing difficulty	Steep learning curve Need for dissection of a large subcutaneous flap Longer operative time Unique complications (e.g., brachial plexus, injury, anterior chest paresthesia) High cost

The extent of subcutaneous dissection required for accessing the neck is another minor drawback. Despite the area of the subcutaneous flap raised being 3–4 times that for the cervical open approach, however, this increased area of flap does not necessarily translate into increased pain or paresthesia [19]. There is though a risk of anterior chest paresthesia, but it is temporary in most cases [45].

The longer operative time associated with robotic transaxillary thyroidectomy is usually reduced once the learning curve is sufficiently overcome [22]. Moreover, the added operative time has not been shown to cause any adverse effect on patient outcome, quality of life, or length of hospital stay [19].

A disadvantage uniquely associated with transaxillary approach is the rare complication of brachial plexus injury. Brachial plexus injury, however, is mostly transient, and preventable with proper arm positioning and the use of somatosensory evoked potential (SSEP) monitoring, as discussed earlier.

A persistent concern is the relatively high cost associated with robotic transaxillary thyroidectomy, which could be a prohibitive factor in many patients. In one study [21], the average cost of a robotic hemithyroidectomy was reported to be $11,905 ± $5924 ($4178–$32,714), and the average cost of a robotic total thyroidectomy was $13,287 ± $8820 ($5125–$42,444). With decreasing operative times and increasing case volume at institutions, the overall financial burden may be reduced in the long run [49].

Advantages and disadvantages of robotic transaxillary thyroidectomy are summarized in Table 18.2.

Future Directions

Since this technique was introduced and pioneered by the South Korean group 10 years ago, robotic transaxillary thyroidectomy has been adopted, modified, and proven to be equal to conventional or endoscopic thyroidectomy techniques. The well-established safety and efficacy of this technique and the outstanding cosmetic

outcomes, along with other advantages, are worth noting and may continue to attract more interest in this technique.

Advancements in robotic technology and development of more sophisticated robotic tools will further enable surgeons to perform more complex neck surgeries with improved precision, dexterity, and safety while reducing operative time [45]. It is conceivable that streamlined surgical robots designed specifically for head and neck surgery, with greater flexibility and a smaller footprint, may someday replace the current robotic system. Areas of added functionality may include incorporation of intraoperative neuromonitoring, improved haptic feedback, and a visualization-navigation system for parathyroid glands, RLN, and lymph nodes. Such advancements in surgical robot functionality may make robotic thyroidectomy even safer and more effective.

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Chapter 19
Transoral Thyroidectomy

Mohammad Shaear and Jonathon O. Russell

Introduction

The practice of surgery in general and thyroid surgery in particular has made significant strides since the nineteenth century [1–3]. Thyroid surgery advanced to become "the pinnacle of the surgeon's art" due to such pioneers as Billroth, Kocher, Halsted, and others [4, 5]. Currently, thyroid surgery is one of the most common procedures performed, with a low rate of complications and generally excellent oncologic outcomes [6]. Importantly, there is no evidence that more aggressive initial treatment (e.g., prophylactic central neck dissection, total thyroidectomy in small cancers, liberal use of radioactive iodine, etc.) will significantly improve disease-specific survival in most thyroid cancers [7–13].

Because disease outcomes are so good, surgeons strive to continue to improve surgical results by reducing morbidity and adding value. Surgeons who seek to reduce morbidity and add value focus on multiple fronts. New objectives include decreasing costs, improving efficiency, and maximizing cosmesis [14–17]. Indeed, even the impacts of surgery on the surgeon have been central to improvement recommendations with recent ergonomic advancements [18, 19]. The reliably superior outcomes of traditional thyroid surgery encourage modifications of even such details as the location of the incision.

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M. C. Singer, D. J. Terris (eds.), *Innovations in Modern Endocrine Surgery*,
https://doi.org/10.1007/978-3-030-73951-5_19

Because the standard Kocher incision leaves a permanent cervical scar (Fig. 19.1), moving this scar to a less visible location offers cosmetic advantages [20]. Many have demonstrated that the presence of a cervical incision affects the health-related quality of life (HRQOL) significantly and may result in self-consciousness [21–25]. Consequently, this neck scar may drive some patients to consider scar revisions years after the initial surgery [22]. Furthermore, there is evidence that others perceive those with a cervical incision as having a lower HRQOL, finding them less attractive than peers without a cervical incision [20].

Although multiple attempts were made to bypass the cervical incision when performing thyroid surgery, few remote-access techniques have gained wide acceptance in the West. Asian countries, however, have found success with the transaxillary (TA), bilateral axillo-breast approach (BABA), and retro-auricular (RA) techniques among others. North America and Europe have been slower to adopt these techniques. In a review completed by the American Thyroid Association, Berber and colleagues found that the lack of broad Western adoption was due to several factors including safety concerns, cost, and patient-related factors such as increased obesity in Western patients [26–30].

In September 2007, the New European Surgical Academy (NESA) proposed transoral thyroid surgery as part of their natural orifice surgery project to investigate what could be safely accessed transorally and transvaginally (NOS/NOTES) [31–33]. One goal of this interdisciplinary effort was discovering a new technique to access the thyroid. These efforts ultimately led to Anuwong publishing his first case series of 60 patients managed with transoral thyroidectomy. Following that, multiple North American and international case series followed to further confirm the potential of TOETVA as the only remote-access thyroid surgery with absolutely no cutaneous incisions (Figure 19.2a–c) [34].

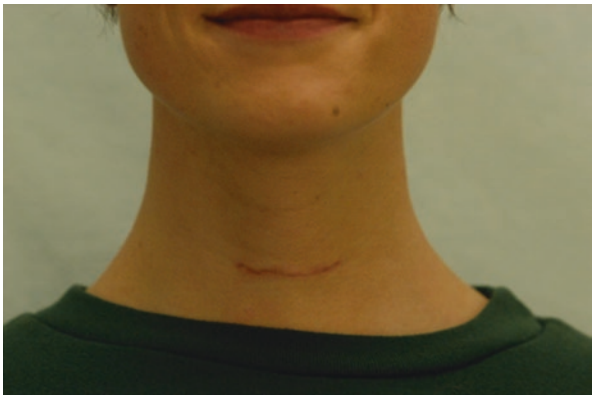

Fig. 19.1 Transcervical incision 1-month following total thyroidectomy in a 25-year-old female

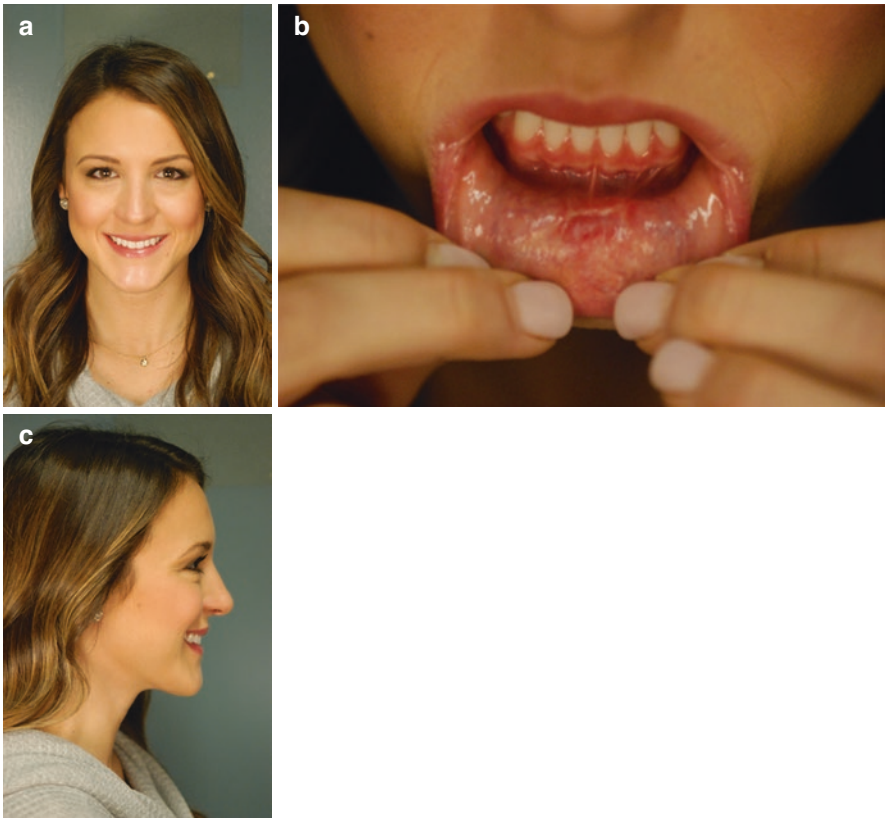

Fig. 19.2 Three weeks after TOETVA in a young female. (**a**) Full face. (**b**) Healing of the vestibular incisions in the mucosa of the mouth. (**c**) Right side of the face and the neck

Remote-Access Thyroid Surgery

Overview

The advancements of endoscopic surgery along with the desire to avoid a neck scar were the driving forces behind the emergence of the initial thyroid technique which focused on improved cosmetic outcomes. Miccoli, inspired by Gagner's report on endoscopic parathyroidectomy, introduced minimally invasive video-assisted thyroidectomy (MIVAT) to the field [35–37]. This technique could not avoid a neck scar but instead offered a smaller incision size. Later, Ohgami et al. published a report describing endoscopic thyroidectomy via the breast approach which was among the first descriptions of remote-access thyroid surgery [15]. Numerous remote-access techniques were then

Table 19.1 Previously described techniques of remote-access thyroid surgery: time of adoption, advantages, and disadvantages

Remote-access thyroid approaches	Technique	Time of adoption	Advantage	Disadvantage
Breast	Endoscopic	2000	First remote-access technique developed	Amount of dissection and CO2 insufflation
Bilateral axillo-breast approach	Robotic and endoscopic	2007	Midline access	Amount of dissection, steep learning curve, and CO2 insufflation
Axillary approach	Robotic and endoscopic	2000	Direct exposure to the ipsilateral thyroid and no CO2 insufflation needed, exposure of the contralateral lobe is possible	Steep learning curve and challenging contralateral lobe
Facelift approach	Robotic and endoscopic	2011	Flap distance is the shortest and CO2 insufflation is not necessary	Top-down view of the thyroid; access to the contralateral side is limited

introduced. While not minimally invasive in the truest sense, they move the incision to a more distant site that is less cosmetically troubling. For instance, the areola and axillary folds were used in the endoscopic breast approach, axillo-bilateral breast approach, and bilateral axillo-breast approach (BABA). With the introduction of robotic surgery, transaxillary and facelift robotic approaches were attempted and have become common in some regions [38–40]. In the end, BABA, robotic transaxillary, and facelift robotic approaches have become favored among the many remote-access thyroid surgeries [30]. The American Thyroid Association statement on remote-access thyroid surgery provides further details and classification of these remote-access techniques as shown in Table 19.1.

Limitations of the Previously Described Remote-Access Thyroid Surgery

The adoption of these remote-access techniques has been slow in the West due to multiple factors such as cost, operative time, learning curve, and technical skills required to successfully utilize these techniques. Moreover, each of these techniques still requires a cutaneous incision.

Development of Transoral Thyroid Surgery

In 2011, Richmon et al. described a tri-vestibular approach to the thyroid compartment using a submental and subplatysmal approach [41, 42]. Nakajo et al. published a case series of eight patients who underwent thyroid surgery via the mouth and without CO2 insufflation. He named the technique “transoral video-assisted neck

surgery" (TOVANS). All eight patients who underwent TOVANS experienced mental nerve injury [43].

Following the route described via the tri-vestibular approach, Anuwong published a cases series of 60 patients who underwent transoral endoscopic thyroidectomy vestibular approach (TOETVA) with promising short-term results in 2016 [34]. Two years later, he expanded his case series to 425 patients with the similar excellent outcomes [44]. This was followed by smaller case series from North America and additional international series [28, 45–47]. To date, approximately 1000 cases of transoral thyroid surgery via the vestibular approach have been reported, with the majority having been performed using the endoscopic technique. A similar technique, utilizing the surgical robot, has been described [48, 49].

The Value of Avoiding a Cervical Incision

While many patients and surgeons have sought alternatives to the standard Kocher incision to provide better cosmetic outcomes, little is known about how a thyroidectomy scar affects health-related quality of life (HRQOL). What little data is available is mostly parsed from larger studies focused on alternative topics, such as overall quality of life. Goldfarb and colleagues have completed several long-term studies examining the impact of thyroid surgery on HRQOL. They have demonstrated that a cervical incision does affect HRQOL to a variable degree, especially among young women [24]. More recent research has demonstrated that the most common adverse event following thyroid surgery relates to the cervical incision, with more than 77% of patients expressing some concerns about cosmesis [25].

When researchers specifically ask patients about their cervical incision, it has been reported that the presence of a scar, no matter how well it heals, affects HRQOL as much as psoriasis, vitiligo, or severe atopic dermatitis [21]. In one study of patients in the United States, only 51% of patients felt that their thyroid scar is "excellent," while more than 10% of patients consider scar revision even years after their initial surgery [22].

More recently, it has been demonstrated that casual observers have negative perceptions of patients with a neck scar. In one study, observers looking at pictures of patients with and without neck scars rated those with scars as less attractive and perceived that they had a lower quality of life. These observers were willing to pay more than $10,000USD to avoid a cervical incision [50]. All of this data suggests a potential opportunity for surgeons seeking to improve outcomes from thyroidectomy.

The Role of Robotic Surgical Systems in Transoral Thyroid Surgery

Given the efficacy of TOETVA, some authors, including our group, have explored the feasibility of adding surgical robotics through the transoral robotic thyroidectomy vestibular approach (TORTVA). In our series, the median operative time was

longer in the robotic group compared to the endoscopic group (322 minutes vs 188 minutes, $P = 0.001$). Two robotic cases needed to be converted to open, and one was converted to the endoscopic approach [51]. The use of drains was more in the robotic group. These results discouraged us to use the robotic technique with the current available options. However, we believe the single-port robotic systems might perform better than their formers.

Surgical Technique

Both the robotic and endoscopic approaches are completed in much the same fashion. The patient is placed supine with slight neck extension, unless the patient is a male in which case the neutral position is utilized so as to avoid making the thyroid cartilage more prominent. Three incisions are made to access the subplatysmal space. The midline incision is made at the distal tip of the buccal mandibular frenulum and measures 15 mm in length and is used for the endoscopic camera and later for specimen retrieval. The other bilateral incisions are made at the junction of the wet-dry border in the lateral oral commissure and measure 5 mm in length, serving as the operating ports for instrumentation (Fig. 19.3). It is important to use caution when creating access to the subplatysmal space in order to not to perforate the skin. We place each of these ports

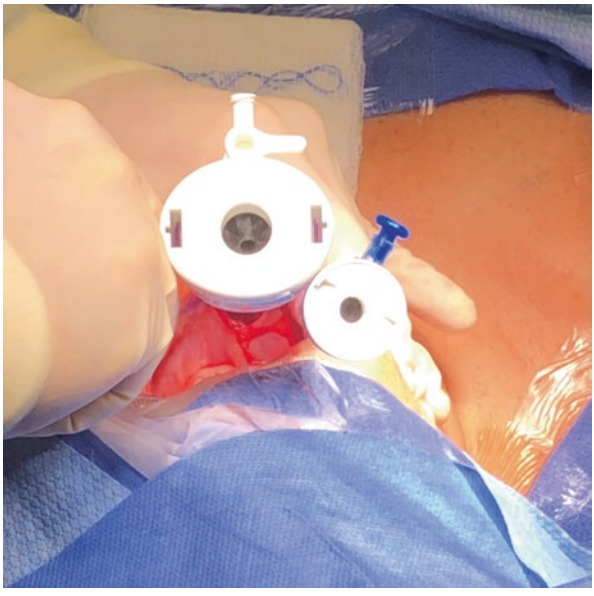

Fig. 19.3 During the insertion of endoscopic trocars in the vestibule of the mouth

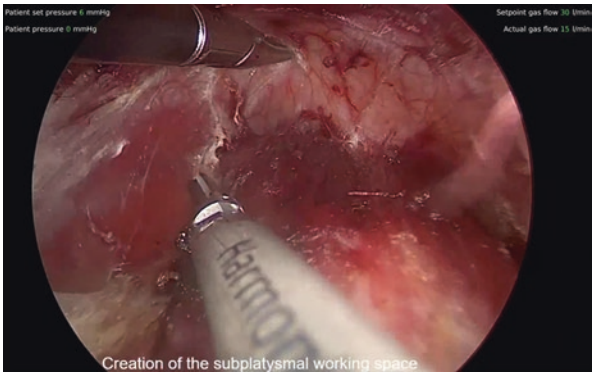

Fig. 19.4 Subplatysmal working space

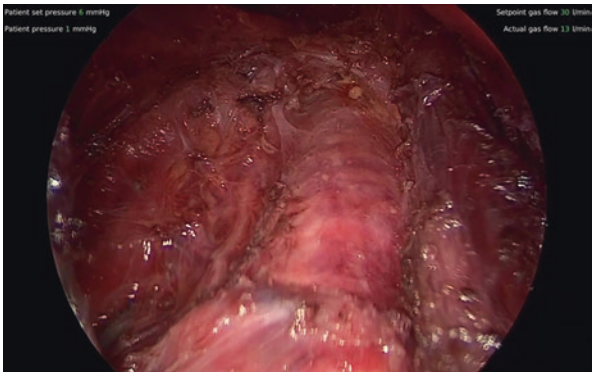

Fig. 19.5 Visualization of the recurrent laryngeal nerve (RLN) after removal of the specimen

bluntly and do not use electrocautery. After creation of the subplatysmal working space, CO2 insufflation at a level of 6 mmHg is initiated to maintain the working space and ventilate (Fig. 19.4). The robot can be docked if desired. The median raphe is then identified and divided to allow elevation of the strap muscles and exposure of the thyroid. The pyramidal lobe and Delphian node are removed to allow visualization of the thyroid cartilage, cricothyroid membrane, and cricoid cartilage. Upon identification of the isthmus of the thyroid, a pretracheal plane is developed and the isthmus is divided. The lobectomy is carried out in a cephalocaudal fashion after identification and preservation of the parathyroid glands and recurrent laryngeal nerve (Fig. 19.5). The specimen is placed in an endocatch bag and removed using the central incision. The contralateral lobe is then removed in the same fashion, and all incisions are closed using dissolvable sutures (Fig. 19.6).

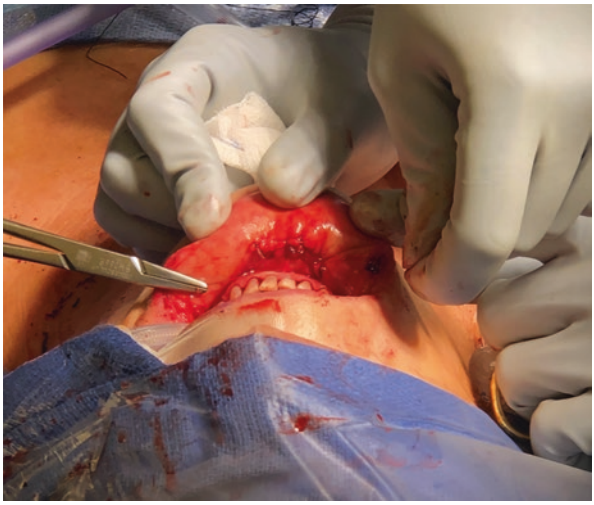

Fig. 19.6 Closure of incisions

Limitations of TOETVA

In contrast to other remote-access thyroid surgery techniques, TOETVA has expansive operative indications. Absolute contraindications include nodules more than 6 cm and lobes more than 10 cm in size. Additional exclusions include a history of head and/or neck surgery or irradiation and patients who are unfit for surgery due to other comorbidities or intolerance to general anesthesia. Clinically, lymph node metastasis or evidence of extrathyroidal extension acts as a relative contraindication. Other relative contraindications include preoperative recurrent laryngeal nerve palsy, recurrent goiter, hyperthyroid status, oral infections, and previous jaw surgeries. TOETVA is an excellent option for patients with a history of abnormal wound healing, such as hypertrophic or keloid scarring, or those who are motivated to avoid a neck scar [52, 53].

Future Directions

In response to the American College of Surgeons 1994 statement on emerging surgical technologies, Perrier ND et al. provided a framework for a systematic approach to robotic thyroidectomy as a novel technique to guide interested surgeons during the implementation phase [54, 55]. Recently, a joint publication established a framework for safely exploring TOETVA [56].

Outcomes from multiple groups and coalitions are imperative to further demonstrate the safety of TOETVA. Likewise, long-term follow-up for oncologic efficacy will be important to confirm that this technique is equivalent to the standard approach. Instrumentation improvements are vital to ensure that surgeons can

rapidly learn and master this new approach. Finally, much remains to be defined regarding the value of avoiding a scar. Despite the limitations in current knowledge, it is apparent that TOETVA offers patients improved outcomes and lower morbidity in the management of thyroid pathology [57, 58].

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Part V
Postoperative Management

Chapter 20
Ambulatory Endocrine Surgery

Kelvin Memeh and Peter Angelos

Introduction

Ambulatory endocrine surgery refers to any endocrine surgical procedure that does not lead to inpatient admission or an overnight patient stay in the facility [1]. Historically, the driver for ambulatory surgery, in general, has been several government policies in response to the rising healthcare expenditures [2]. By far, the most influential of these policies was the Social Security Act Amendment of 1983 [3]. The act empowered Medicare to incentivize reimbursement for care provided in the outpatient setting compared to similar operations performed in inpatient facilities. This initiative gained the support of other health insurance organizations and, to a large extent, the support of physician groups, notably the American Medical Association, the American Society of Anesthesiologists, and the American College of Surgeons. These physician groups developed and endorsed clear guidelines and standards of practice for ambulatory surgical centers (ASC) in the early 1970s.

Concurrently, innovations in anesthesia and surgical techniques that facilitated safer surgery during this period were adopted. The current state of ambulatory surgery is, therefore, a product of necessity to cut costs paired with innovations in medicine. These innovations have ensured safe same-day discharge after surgery. However, despite these innovations, the safety of ambulatory surgery has remained controversial, especially in the subspecialty of endocrine surgery where complications such as post-thyroidectomy neck hematoma and the associated risk of asphyxiation can be rapidly fatal.

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M. C. Singer, D. J. Terris (eds.), *Innovations in Modern Endocrine Surgery*,
https://doi.org/10.1007/978-3-030-73951-5_20

In this chapter, we will review some of the potential benefits and challenges that are specific to ambulatory endocrine surgery. We will also highlight some of the innovations utilized by endocrine surgeons to prevent, minimize, and manage perioperative risks.

Potential Benefits of Ambulatory Endocrine Surgery

One of the strongest drivers for ambulatory surgery is cost savings to patients and healthcare payers. This driver is true for ambulatory endocrine surgery in general, although most studies on the subject have been on ambulatory thyroid and parathyroid surgery. Inhospital facility charges generally increase the cost of performing any surgical procedure. Terris et al. [8] showed that up to $2474 could be saved per case if total thyroidectomy is performed in an outpatient setting. Although this analysis was based on hospital charges and not true reimbursement, similar savings have been reported by other studies [28, 32, 35]. It takes significantly more hospital resources (staff-hour, consumables, hospital beds) to provide care for patients who are admitted after surgery compared to those discharged from the postanesthesia care unit (PACU). In the era of bundled payments, these savings could be significant, given that hospitals could receive the same amount of reimbursement regardless of the admission status of the patient. Also, there are potential cost savings on the side of the patient, as some insurance plans require a co-pay per night, which can be avoided by a safe discharge from the PACU.

Further, some proponents of ambulatory surgery argue that discharge from the outpatient setting may theoretically decrease a patient's exposure to harm that might occur in the inpatient setting. This harm could be in the form of nosocomial infection or medical error. Avoiding these harms may contribute to significant cost savings for all parties involved. Given that there are large numbers of reported medical errors in hospitals each year [6], proponents of ambulatory surgery argue that encouraging outpatient care may potentially reduce the incidence of these errors and save money for healthcare payers, patients, and hospitals.

Another potential benefit of ambulatory endocrine surgery is patient comfort and satisfaction. We find that patients are generally open to the concept of same-day discharge as they appreciate the idea of going home and recovering in the familiar setting and comfort of their homes. This is especially true if there has been preoperative discussion to set this expectation. Perhaps one of the most interesting studies on the subject compared preferences for same-day discharge among patients who underwent thyroidectomy/parathyroidectomy and those who underwent laparoscopic cholecystectomy [13]. They reported that 65% of patients who underwent outpatient thyroidectomy/parathyroidectomy were satisfied with outpatient surgery and would not have preferred to stay in the hospital whereas 35% would have preferred inpatient admission after their surgery. The numbers were nearly identical for

patients who underwent outpatient cholecystectomy. They concluded that outpatient thyroidectomy/parathyroidectomy is equally as acceptable as other well-known outpatient procedures like cholecystectomy.

Ambulatory Thyroid Surgery

Despite the landmark publication by Steckler et al. in 1986 [4], advocating for outpatient thyroidectomy, some high-volume thyroid surgeons continued to oppose the idea of outpatient thyroid surgery due to patient safety concerns [5]. Steckler argued that in carefully selected patients, outpatient thyroid surgery was safe, comfortable for patients, and cost-efficient. It was not until the turn of the millennium that ambulatory thyroid surgery started to gain widespread traction, first with thyroid lobectomy and then parathyroidectomy for primary hyperparathyroidism.

Challenges and Risks of Ambulatory Thyroid Surgery

Most surgeons still admit patients after total thyroidectomy and completion thyroidectomy. This practice continues despite the potential benefits of ambulatory thyroid surgery. The concern is that there is an increased risk of post-thyroidectomy complications in this patient group [7]. Below, we discuss some of the common risks after thyroidectomy and the techniques that have emerged to minimize or prevent them.

Recurrent Laryngeal Nerve Injury and Risk of Aspiration

The incidence of recurrent laryngeal nerve (RLN) injury is about 1% or less in the hands of experienced thyroid surgeons. Although injury to the RLN is rare, it is potentially life altering, and so thyroid surgeons exercise extreme caution during dissection of the nerve. To assess nerve integrity, some surgeons employ conventional visual assessment only. However, the drawback of the visualization-only technique is that anatomical and functional integrity of the nerve do not always correlate. Therefore, a structurally intact RLN does not guarantee normal RLN function [9]. To this end, most surgeons have incorporated the use of neuromonitoring as a way of confirming the functional integrity of the nerve during surgery. Some studies (including meta-analyses) have evaluated both nerve preservation techniques and have found no significant difference in the rate of RLN injury with either technique [9, 10]. However, newer data suggest that neuromonitoring may reduce the incidence of both transient and permanent RLN injuries [11, 12]. To our knowledge, there is no difference in the incidence, recognition, and management of injury to the RLN based on the setting of the operation (inpatient vs ambulatory). However, the

use of RLN monitoring provides the surgeon with real-time knowledge and assurance of nerve integrity. Loss of electromyographic signal alerts the surgeon to a potential nerve injury. Given that unilateral RLN injury inevitably leads to vocal cord paresis or paralysis, which can potentially lead to aspiration from glottic insufficiency, this information allows the surgeon to proactively coordinate laryngoscopic examination and possible intervention immediately after surgery or at least provide aspiration precautions should the patient have a normal voice upon full awakening. Also, in the event of a unilateral nerve injury, as suggested by loss of signal, the surgeon can avoid bilateral RLN injury by not proceeding to the contralateral side. Therefore, in our opinion, the use of neuromonitoring is critical to the success of a safe ambulatory thyroidectomy practice.

Post-Thyroidectomy Neck Hematoma and Risk of Asphyxiation

The most significant challenge to ambulatory thyroid surgery is the concern for post-thyroidectomy neck hematoma (PNH). The actual incidence of PNH is difficult to establish because of the variability in reporting and the relatively low incidence of the complication itself. Generally, experienced thyroid surgeons quote a less than 1% risk of neck hematoma following total thyroidectomy; however, this risk can range from 0.1% to up to 6.54% [1, 14–16]. The most concerning aspect of PNH is its potential to cause asphyxiation from relatively rapid compromise of the airway.

Over the years, many techniques have been incorporated into thyroid surgery to either enhance hemostasis or minimize the impact of a potential PNH. These include the use of surgical drains, the use of hemostatic devices and agents, and new anesthesia techniques. While some of these techniques may facilitate ambulatory surgery, the utility of others remains unclear. The use of surgical drains, for instance, has been exhaustively investigated, and the general understanding from those trials is that drains may help evacuate hematoma and perhaps bring PNH to the surgeon's attention. However, they do not prevent neck hematoma requiring surgical intervention [15, 16]. Also, patients who have drains placed during thyroidectomy are usually (and appropriately) admitted for observation.

Another surgical technique that may prevent life-threatening PNH is limited reapproximation of the strap muscles [17]. While this technique does not prevent hematoma, it allows the hematoma to decompress into the subcutaneous space rather than collecting in a "sealed" compartment around the airway. This minimizes the compressive effect on the larynx, which usually starts the cascade of events that can lead to laryngeal edema and obstruction.

Energy devices such as the Harmonic Scalpel (Harmonic Focus; Ethicon, Johnson and Johnson, Cincinnati, OH, USA) and LigaSure (LSJ Medtronic, Covidien product, Minneapolis, MN, USA) have been reported to improve hemostasis and decrease operative time with no difference in post-thyroidectomy complications [18, 19]. Thus, thyroid surgeons have long incorporated these devices into their practice. However, there is no convincing data that these devices reduce the incidence of PNH.

Similar to energy devices, there are a plethora of bioabsorbable agents that are available, which promote hemostasis. These include oxidized cellulose mesh, topical thrombin gel, fibrin sealant, and compressed foam. The effectiveness of these agents has been evaluated either alone or in combination with energy devices in various randomized trials. Hemostatic agents reduce operative time, time to drain removal, and hospital length of stay after thyroidectomy, but they do not decrease the incidence of PNH [20, 21]. One can, however, infer from these randomized trials that the use of hemostatic agents should be a necessary technical component in an ambulatory thyroid surgery practice. Less time spent in the operating room may maximize the time spent in the PACU for monitoring, which could impact the decision regarding same-day discharge.

An anesthetic technique that may reduce the incidence of PNH is deep extubation (DE). DE involves the removal of the endotracheal tube while the patient is still fully anesthetized, to reduce emergence issues such as coughing, strain, and hemodynamic stress [22]. DE was initially used as an adjunct to decrease the risk of bleeding after neurological and ophthalmic surgery but is now increasingly being adopted by anesthesiologists for thyroidectomy patients. Thyroidectomy patients are typically good candidates for DE, given that they are typically not paralyzed to allow for the use of neuromonitoring. There is a paucity of data to suggest that DE directly reduces the incidence of PNH. However, from a mechanical standpoint, it might; hence, it is one of the measures suggested by the American Thyroid Association (ATA) in its statement on ambulatory surgery [1].

It is important to note that it is difficult to predict the time interval between surgery and development of PNH or which PNH will eventually progress to become life-threatening.

It is, therefore, imperative that surgeons be aware of the risk factors that predispose patients to develop PNH. Surgeons can recommend closer monitoring for these patients or exclude them from outpatient thyroidectomy all together. Signs and symptoms suggestive of PNH include diffuse swelling under the incision in the anterior neck, a sensation of tightness, and purple discoloration of the skin [1]. Late signs of PNH include respiratory distress and stridor. Understanding the timing and sequence of these signs, as well as proper patient selection based on their risk factors, is fundamental to the successful implementation of an ambulatory thyroid surgery program. In a multicenter study evaluating the timing and the risk of PNH in 207 patients who required evacuation of a PNH after thyroidectomy, Campbell et al. [23] reported the following factors to be independently associated with PNH: use of a drain (odds ratio, 2.79), Graves' disease (odds ratio, 2.43), benign pathology (odds ratio, 2.22), antiplatelet/anticoagulation medications (odds ratio, 2.12), use of a hemostatic agent (odds ratio, 1.97), and increased thyroid mass (odds ratio, 1.01). Of note, they found that most hematomas (79%) developed within 24 hours of surgery, with 47% of them developing in the first 6 hours after surgery. The findings of this study are similar to those of Leyre et al. [24] and Promberger et al. [25]. These studies suggest that most PNH would develop within 24 hours of surgery. Although associated airway compromise from PNH was not fully evaluated in these studies, one could infer that more severe bleeding that may pose a higher risk of asphyxiation would occur early and that later PNH would more likely result from less

Table 20.1 Exclusion criteria for ambulatory thyroid and parathyroid surgery reported

By selected studies
Patient factors and demographics
Age >75 years old [27]
Patients living in remote regions or too far from operating hospital [27, 31]
Language barrier [31]
Patient preference [29, 31]
Lives alone or lack of autonomy or social support [27, 28, 31]
Nature of surgery and thyroid disease
Advance thyroid cancer (T4) [34]
Toxic adenoma [27]
Lymph node dissection [29, 33, 34]
Reoperation [29] or previous neck radiation [34]
Completion surgery [27]
Concomitant procedure [28, 31, 33, 34]
Need for drain [8, 28]
Patients comorbidities
Comorbidity that needs postoperative monitoring [28, 29]
ASA ≥3 [27, 34]
OSA [27]
Anticoagulation [28, 31]

dramatic bleeding unlikely to cause airway compromise. Based on this premise, we argue that low-risk patients who remain without PNH can be safely discharged after a reasonable period of observation in the recovery room, usually 6 hours. To this end, some authors have laid out strict criteria for patients considered inappropriate candidates for ambulatory thyroid surgery, as shown in Table 20.1 [10, 27–29, 31–34].

Hypoparathyroidism and Risk of Severe Hypocalcemia and Tetany

Post-thyroidectomy bleeding and hematoma dominate the conversation for and against ambulatory endocrine surgery. However, hypoparathyroidism is the most frequent complication following thyroidectomy. It is reported to occur in up to 30% of patients undergoing total or completion thyroidectomy [39, 40]. In a multicenter audit by Bergenfelz et al. [41], the incidence of temporary and permanent hypoparathyroidism was 9.9% and 4.4%, respectively. However, there is considerable variability in the diagnostic criteria for post-thyroidectomy hypoparathyroidism across studies. One study reported a rate as low as 6% for transient hypoparathyroidism and 1–2% for permanent hypoparathyroidism [42]. Regardless of the disparity in the reported rate of post-thyroidectomy hypoparathyroidism, there does appear to be a correlation with surgeon volume and lower rates of this complication [42–44]. The main issues with postoperative hypoparathyroidism are patient discomfort, risk of tetany, and readmission for treatment and monitoring.

Just like in its diagnosis, there is considerable disparity in the management of postoperative hypoparathyroidism. Some surgeons routinely discharge patients with calcium supplementation, with or without vitamin D [45, 46]. In contrast, other

surgeons adopt a more risk-stratified approach based on intact parathyroid hormone (iPTH) levels in the PACU [40, 49–51]. Several studies support routine supplementation, in which case a combined calcium and vitamin D supplementation seems to be more effective than calcium alone [45–48]. However, there are also data to support the use of iPTH levels to risk-stratify patients. Interestingly, iPTH levels obtained within 4 hours of surgery are equally predictive of postoperative hypocalcemia compared to levels obtained 1 day after surgery [49–52].

In our experience, patients with iPTH levels <10 pg/dl in the postoperative period are likely to develop symptomatic hypocalcemia and so require prophylactic supplementation with both vitamin D and calcium. Patients with iPTH levels >20 pg/dl are unlikely to develop symptomatic hypocalcemia and so can be discharged without supplementation. For patients with iPTH levels between 10 and 20 pg/ dl, we routinely supplement them with calcium, with or without vitamin D [52]. This approach has been supported by other studies [49–51]. With this knowledge, surgeons can more confidently discharge patients with the appropriate postoperative calcium management.

Postoperative Pain, Nausea, and Vomiting

One of the challenges of ambulatory endocrine surgery is the management of postoperative nausea and pain. In the early twentieth century, thyroidectomies were performed utilizing local anesthesia mostly because of the morbidity and mortality associated with general anesthesia at the time. As general anesthesia became safer, surgeons gravitated to its use, citing patient comfort and the ability to have a motionless surgical field.

However, one of the main challenges of general anesthesia for thyroidectomy is postoperative nausea and vomiting (PONV). PONV is common after thyroidectomy and poses a challenge to ambulatory thyroidectomy. This is because patients need to feel comfortable before discharge. Additionally, PONV has been associated with increased risk of PNH [15].

To avoid these issues, some surgeons have employed the use of local/regional anesthesia instead of general anesthesia. Paul LoGerfo, one of the foremost pioneers of ambulatory endocrine neck surgery, published an initial series of 206 thyroidectomies performed using local/regional anesthesia in the ambulatory setting [30]. His report demonstrated that the approach was safe with comparable morbidity and high patient satisfaction. Spanknebel et al. [31], in a follow-up study of 1025 patients undergoing partial and total thyroidectomy and parathyroidectomy, showed that 96% of these operations were performed under local anesthesia with patients discharged to home on the same day of surgery. Of note, 90% of the patients in this study were relatively healthy with ASA classification of two or less. Interestingly, outpatient thyroidectomy using local/regional anesthesia was shown to provide cost savings compared to thyroidectomy with general anesthesia [32]. These results were further buttressed by two subsequent randomized trials evaluating outcomes of local vs general anesthesia for thyroidectomy [33, 34].

Despite the successes of these groups, most thyroidectomies in the USA today are still performed under general anesthesia.

Several studies have shown that the preoperative administration of dexamethasone significantly reduces postoperative nausea and vomiting after thyroidectomy [36–38]. In a systematic review and meta-analysis, Li et al. [36] analyzed seven randomized control trials (RCT) comparing the effect of single-dose preoperative dexamethasone against no dexamethasone on the incidence and severity of PONV and postoperative pain. They reported a statistically and clinically significant difference in the incidence and severity of PONV in favor of dexamethasone use. So, for surgeons utilizing general anesthesia, the use of preoperative dexamethasone is recommended to help reduce PONV that may prevent discharge to home from PACU.

It is important to stress that appropriate patient selection is the most critical factor that predicts a successful ambulatory thyroid surgery practice. We also preemptively discuss the possibility of admission with patients given the fact that the ultimate decision on discharge is predicated upon the events during and immediately after surgery. This discussion helps patients prepare for the unlikely events of an overnight admission and hopefully helps to improve their hospital experience.

Given all of the innovations that have ensured safe thyroidectomy, it is no surprise that there is an uptrend in thyroidectomy performed on an ambulatory basis. McLaughlin et al. [26] reviewed 76,604 partial and total thyroidectomies entered into the American College of Surgeons National Surgical Quality Improvement Program (ACS-NSQIP) database between 2005 and 2014. The authors reported a clear trend toward outpatient thyroidectomy (both partial and total) over the period. Interestingly, the authors reported no statistically significant difference in the incidence of reoperation (1.9%) and unplanned 30-day readmission (1.4%) between outpatient and inpatient thyroid surgeries, although sicker patients had inpatient cases.

Ambulatory Parathyroid Surgery

Historically, the risk of postoperative complications after parathyroidectomy was similar to those of thyroidectomy. As bilateral neck exploration for parathyroidectomy was standard, parathyroid patients frequently underwent a similar level of surgical dissection and exploration as thyroid patients. Consequently, parathyroid patients were admitted for observation after surgery.

However, with the increasing adoption of focused parathyroidectomy, surgeons are now more confident in performing parathyroidectomy in the ambulatory setting [53]. These focused surgeries markedly reduce the risk of postoperative complications, including hypoparathyroidism and RLN injury.

It is important to note that for patients with very high calcium levels or with long-standing primary hyperparathyroidism, there may be concerns of developing severe symptomatic hypocalcemia after surgery secondary to “hungry bone syndrome.” In general, we employ a risk-stratified approach in this patient group. For those who

undergo a single-gland parathyroidectomy with an appropriate drop in intraoperative iPTH, we generally feel confident in discharging them from the PACU as long as their PACU iPTH levels are >20 pg/dl. Often, they will be discharged with calcium supplementation and arrangement for a calcium and PTH check within 72 hours of surgery.

Conclusion

Ambulatory endocrine surgery, a product of the necessity to decrease healthcare expenditures, has been sustained by innovations in medicine and fostered by changing patient preferences. Despite the significant innovations in medicine that have ensured safe same-day discharge after surgery, the concept of ambulatory endocrine surgery may remain controversial given the potentially life-threatening nature of some of the complications inherent in these procedures. Crucial to the success of an ambulatory endocrine surgery practice is careful patient selection.

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Chapter 21
Postoperative Calcium Management

Guy Slonimsky and David Goldenberg

Introduction

Parathyroid hormone (PTH) regulates serum calcium levels through three mechanisms: facilitation of bone resorption, 1,25-dihydroxyvitamin D production by the kidneys, and intestinal absorption [1]. Compromised secretion of PTH results in hypocalcemia. Hypoparathyroidism with resulting hypocalcemia is the most common complication of thyroid and parathyroid surgery (total thyroidectomy, completion thyroidectomy, and parathyroidectomy). It is a "metabolic/endocrine" complication of thyroid and parathyroid surgery and is manifested as temporary or permanent hypoparathyroidism. Hypoparathyroidism persisting for over 6–12 months following surgery is classified as permanent [2, 3]. The majority of postsurgical hypoparathyroidism cases are transient; however, occasionally it leads to prolonged hospitalization and lifelong calcium supplementation. The reported range varies widely up to 38% for transient hypoparathyroidism, and 3% for permanent hypoparathyroidism [2, 4–10]. The underlying surgical pathophysiology is typically direct injury or devascularization of the parathyroid glands as a result of dissection, cauterization, or unintended avulsion.

It is well recognized that the risk of postoperative hypoparathyroidism is directly proportional to the extent of the surgery (e.g., the extent of neck exploration in parathyroid surgery, total vs partial thyroidectomy, resection of a large goiter, the addition of neck dissection, specifically of the central compartment) and the presence of autoimmune thyroid disease (Hashimoto's thyroiditis and Graves' disease) [11] and

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M. C. Singer, D. J. Terris (eds.), *Innovations in Modern Endocrine Surgery*,
https://doi.org/10.1007/978-3-030-73951-5_21

inversely proportional to the surgeon's experience [5, 8, 9, 12–20]. Inadvertent resection of parathyroid glands, parathyroid gland auto transplantation, the identification and preservation of fewer than two parathyroid glands during total thyroidectomies, heavier thyroid specimens, revision surgery, and reoperation due to bleeding were also found to be risk factors for postoperative hypoparathyroidism [5, 21–23].

Patient and Disease Predisposing Risk Factors

Endocrine surgeons should be cognizant of several nonsurgical, patient- and disease-dependent, predisposing risk factors for postoperative hypocalcemia. Stratifying the patient's risk for postoperative hypocalcemia has the potential to anticipate, prevent, and improve management of this complication. Edafe et al., in a comprehensive systemic review and meta-analysis, reported preoperative 25-hydroxyvitamin D, perioperative PTH levels, and female sex as independent predictors of transient postoperative hypocalcemia. Graves' disease and larger thyroid specimens independently predicted permanent hypocalcemia [5].

Lower preoperative 25-hydroxyvitamin D level results in reduced intestinal calcium absorption as well as increased renal excretion and further contributes to transient postoperative hypocalcemia. Risk factors for low vitamin D levels include malabsorption female gender, obesity older age and dark skin [24].

Another independent risk factor for profound post-thyroidectomy hypocalcemia is previous gastric bypass surgery [2, 25–28]. Following gastric bypass surgery, the ingested food is rerouted to bypass the proximal small bowel, leading to malabsorption of vitamin D and calcium. In cases of inadequate supplementation, patients who undergone gastric bypass surgery tend to remain chronically vitamin D deficient with elevated PTH levels and have a higher incidence of secondary hyperparathyroidism [29]. Additionally, the reduction in gastric acidity following partial gastrectomy results in malabsorption of calcium salts. In a recent study, Moize et al. reported that laparoscopic sleeve gastrectomy results in a comparable incidence of nutritional deficiencies as Roux-en-Y gastric bypass surgery [30]. Due to chronic malabsorptive state, patients with a history of bariatric surgery are at increased risk for severe and intractable hypocalcemia following thyroid/parathyroid surgeries, and therefore may require a more aggressive and prolonged regimen of calcium and vitamin D supplementation. Moreover, some authors advocate for thyroid screening for candidates of bariatric surgery. In case that thyroid surgery is indicated, it should be performed prior to the bariatric surgery [27]. Others recommend a staged thyroidectomy for patients with a history of bariatric surgery when total thyroidectomy is indicated [31].

Patients with chronic vitamin D deficiency may be at greater risk for postoperative hypocalcemia and hungry bone syndrome following parathyroidectomy. However, the benefits of vitamin D repletion prior to surgery for primary hyperparathyroidism are unclear [32–36].

In thyroid surgery, there is lack of consensus regarding whether the level of 25-hydroxyvitamin D deficiency correlates with the degree of postoperative

hypocalcemia [37–40]. Overall, Edafe et al. reported in their meta-analysis that preoperative vitamin D deficiency independently predicts postoperative transient hypocalcemia, and although several studies reported low preoperative calcium as a predictor of postoperative hypocalcemia, these findings were most likely confounded by low levels of vitamin D [5]. The 2018 American Thyroid Association statement on postoperative hypoparathyroidism recommends the correction of vitamin D deficiency prior to bilateral thyroid surgery [3].

Signs and Symptoms of Hypocalcemia

The clinical manifestation of hypocalcemia can vary from an asymptomatic patient to a rapidly deteriorating one with a life-threatening muscle tetany, seizures, and cardiac arrhythmia. Calcium is a key factor in neuromuscular signal transmission and depolarization threshold; hence, reduced serum calcium levels result in increased neuromuscular excitability. Signs and symptoms of hypocalcemia usually correlate with the severity of the serum calcium deficiency level. Subtle symptoms of hypocalcemia can include perioral or fingertip paresthesia. Chvostek's sign (facial musculature twitching upon tapping of the facial nerve over the preauricular region) and Trousseau's sign (carpopedal muscle spasm following forearm ischemia induced by an inflated blood pressure cuff above systolic blood pressure for 3 minutes) are manifestations of increased neuromuscular excitability (Fig. 21.1a and b). Of note, up to 20% of normocalcemic patients may have a positive Chvostek's sign;

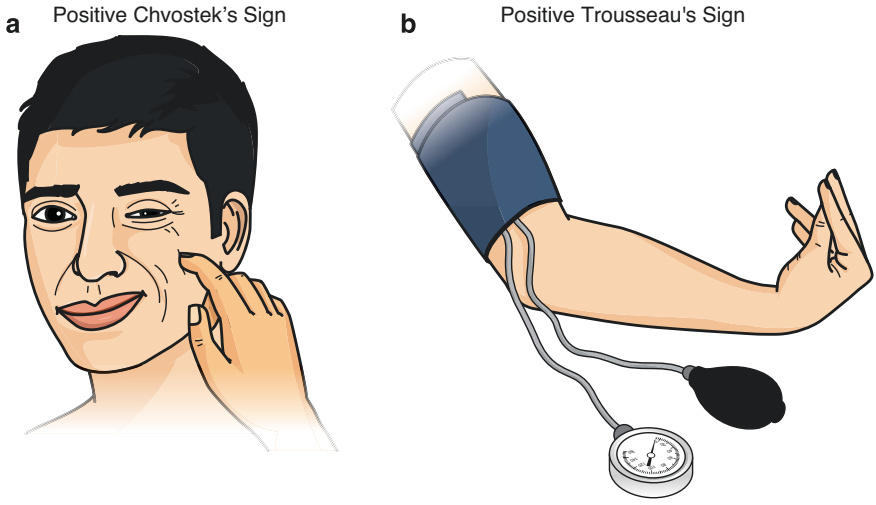

Fig. 21.1 (**a**) Positive Chvostek's sign: left facial muscle twitching upon tapping the region over the main stem of the facial nerve. (**b**) Positive Trousseau's sign: carpopedal contraction following ischemia induced by a sphygmomanometer inflated above the systolic blood pressure for 3 minutes

therefore, evaluating for the presence of Chvostek's sign should be performed during the preoperative evaluation (author's recommendation). Spontaneous muscle cramps and spasms can occur as the serum calcium level further drops. Anxiety, irritability, and other acute mood disorders can be the manifestation of neurocognitive instability. Severe hypocalcemia can eventually result in seizures, laryngospasm, bronchospasm, and lethal arrhythmia (torsades de pointes and ventricular fibrillation) due to QT interval prolongation [1, 2, 41].

Monitoring of Postoperative PTH and Calcium Levels

There are no universal guidelines for the monitoring of serum PTH and calcium levels of patients following thyroid and parathyroid surgeries. Consequently, individual surgeons adopt regimens based on the literature, previous training, experience, and personal preferences. Obviously, adaptations should be made for each individual case based on surgical and patient's risk factor.

Following the successful resection of a single parathyroid adenoma in a focused exploration, the serum calcium level usually drops in 2–3 mg/dL within the first 24–48 hours and stabilizes within the normal range by postoperative days 3–4. In the absence of hungry bone syndrome, these patients usually will not suffer from hypocalcemia due to the remaining parathyroid glands [42].

The common practice of the authors is to perform focused minimally invasive parathyroidectomies in an outpatient setting. PTH assays in these cases are used intraoperatively. No postoperative calcium measurements are performed, unless the patient becomes symptomatic. For patients with multiglandular parathyroid disease requiring the removal of more than a single gland or in those undergoing an extensive bilateral neck exploration with concern for the function of the remaining parathyroid glands, overnight observation with repeated PTH and calcium measurements can be considered. Following uncomplicated thyroid surgeries, the authors usually discharge patients after 24 hours with a single serum calcium measurement performed on the morning prior to discharge. Following surgeries with a concern for the function of the parathyroid glands, or based upon patient's symptoms, earlier calcium checks with possible PTH measurements are performed.

The goal of a single or serial calcium/PTH measurement is to identify existing hypoparathyroidism/hypocalcemia, predict patients at risk for impending hypocalcemia, and direct management. In other words, the absolute serum calcium/PTH levels should be determined as well as the trend of the change evaluated [43, 44]. In order to collect all the aforementioned pieces of data, it is prudent to obtain at least two measurements.

Whether measurements should include total serum or ionized calcium levels and whether to include PTH levels is subject to surgeon preference and the given clinical scenario. PTH levels can aid in prognostication of hypoparathyroidism and

hypocalcemia. Moreover, unlike serum calcium, PTH levels are less likely to vary due to prophylactic calcium and vitamin D supplementation or by low preoperative vitamin D levels. In general, in the case of a hypocalcemic patient for which serial postoperative measurements are necessary, usually a single PTH measurement several hours following surgery, or on postoperative day one, is sufficient for prognostication [43–57].

Prognostication of Postoperative Hypoparathyroidism/ Hypocalcemia

As discussed, the absolute values, trends, and slopes of the calcium and PTH measurements enable the surgeon to stratify patient's risk for hypoparathyroidism/hypocalcemia and to direct management [43–57]. In general, patients who are normocalcemic during the first postoperative day, or who have upsloping serum calcium levels, are less likely to suffer from hypocalcemia [51, 54]. Gulluoglu et al. reported that following bilateral thyroid surgery, patients with a positive or neutral serum calcium slope within the first 14 postoperative hours did not experience hypocalcemia [43].

Asari et al. reported that following thyroid surgeries, serum calcium measurement alone (when not combined with PTH levels) was not reliable for predicting parathyroid metabolism. When the authors applied a calcium cutoff value of 8.42 mg/dL (2.1 mmol/L) on the first postoperative day, normal parathyroid metabolism could be predicted with a sensitivity, specificity, PPV, and NPV of 18.6%, 96.1%, 61.5%, and 77.7%, respectively. On the second and third postoperative days, the sensitivity of serum calcium to predict hypoparathyroidism climbed and reached 72.1%. Moreover, a positive slope of the serum calcium predicted stable calcium levels with a sensitivity, specificity, PPV, and NPV of 88.4%, 35.4%, 31.7%, and 91.0%, respectively [44].

It is well recognized that patients with very low (or undetectable) PTH levels during the first postoperative hours or day are at an increased risk for hypocalcemia [52, 53, 56]. In one study a low, early postoperative PTH measurement (<12 pg/mL) was found to predict hypocalcemia with a sensitivity and specificity of 100% and 92%, respectively [56]. Youngwirth et al. reported that a PTH level lower than 10 pg/mL measured 4 hours following thyroid surgery predicts hypocalcemia and indicates the need for calcium and calcitriol supplementation, in order to prevent potential readmission [55]. Grodski et al. found that patients with a 4-hour, postoperative PTH levels >10 pg/mL can be safely discharged on the first postoperative day with supplemental calcium [57]. Similarly, Selberherr et al. reported that serum PTH >15 pg/mL on the morning of postoperative day one predicts normocalcemia in >99% of cases [45]. Of the patients with serum PTH <15 pg/mL, 38% resumed normal serum PTH levels on the second postoperative day.

Management of Postoperative Hypoparathyroidism/ Hypocalcemia

The management of postoperative hypocalcemia is based mainly on the surgeon's experience and institutional protocols, rather than controlled trials. While some surgeons will prophylactically administer postoperative calcium (with or without vitamin D) supplementation, others may not routinely do so. In general, the approach should aim for maintaining the patient at the lower range of the normal corrected calcium range (approximately 8.0–8.5 mg/dL) while controlling the symptoms and minimizing complications [1, 3].

The approach of prophylactic postoperative administration of oral calcium, sometimes with calcitriol (1,25-dihydroxyvitamin D3, the hormonally active metabolite of vitamin D), has been adopted by many surgeons. As mentioned, transient hypocalcemia is common and may prolong admission and add costs while exposing the patient to potentially preventable side effects. The rationale behind prophylaxis is bridging over the period of the anticipated transient postoperative hypocalcemia. Hypocalcemia symptoms usually manifest within 24–48 hours, and serum calcium levels reach a nadir within 48–72 hours following surgery.

Mild hypocalcemia can be treated with oral supplementation, while in cases of moderate to severe hypocalcemia, intravenous (IV) calcium supplementation may be needed to augment the oral therapeutic protocol. Patients with mild to moderate postoperative hypocalcemia with a serum calcium above 7 mg/dL (with or without mild symptoms) can be supplemented in a similar fashion as the prophylactic protocol of 1–3 grams of daily calcium carbonate (or other equivalent of 1200 mg of elemental calcium) with calcitriol 0.25–0.5 μg every 12 hours [2, 3, 58, 60].

Patients with moderate to severe hypocalcemia (total serum calcium level below 7 mg/dL or ionized calcium below 1.0 mmol/L) should undergo a 12-lead EKG, to asses for QT prolongation or arrhythmias, and remain under continuous cardiac monitoring [3]. Moderate to severe hypocalcemia will require IV supplementation, usually with boluses of 1–2 grams of calcium gluconate. Oral calcium supplementation can be raised to 4 grams daily in 2–3 divided doses, and calcitriol up to 1 μg twice daily if needed [2, 3].

Magnesium was found to be essential for PTH secretion and action [61]. While mild hypomagnesemia stimulates PTH secretion, severe hypomagnesemia results in decreased PTH secretion [62]. In cases of persistent hypocalcemia despite adequate supplementation, magnesium serum levels should also be monitored and orally replenished when below 1.6 mg/dL, with 400 mg of magnesium oxide once or twice daily [2].

In spite of the ability to successfully maintain normocalcemia in patients suffering from postsurgical chronic hypoparathyroidism, these patients are prone to suffer from complications such as altered bone metabolism, soft tissue and urinary system calcifications, and renal failure. Additionally, chronic hypoparathyroidism and requisite oral supplementation negatively impact overall patient well-being and levels of anxiety [1, 2, 63–65].

Natpara, a bioengineered recombinant human parathyroid hormone (rhPTH [1–84]), was FDA approved in 2015 for the treatment of permanent and refractory hypoparathyroidism (of any etiology, other than autosomal dominant hypocalcemia) resistant to conventional therapy with oral calcium and vitamin D supplementation. Natpara administered subcutaneously (50–100 μg once daily) effectively reduced oral calcium and vitamin D supplementation requirements in the majority of hypoparathyroid patients in the REPLACE trial [66]. Moreover, Natpara was found to increase bone turnover and counteract the state of overmineralized bone associated with hypoparathyroidism, therefore leading to more normal bone metabolism [67, 68]. Adverse reactions were reported for less than 3% of patients and included hypocalcemia, hypercalcemia, and hypercalciuria. Importantly, in rats it appeared to be associated with a higher risk of developing osteosarcoma [2, 3, 65, 66, 69–72]. Natpara is distributed and administrated solely by certified pharmacies and providers through the Natpara Risk Evaluation and Mitigation Strategy (REMS) program [72].

Hungry Bone Syndrome

Hungry bone syndrome (HBS) refers to a state of severe and possibly prolonged hypocalcemia, typically following parathyroidectomy, due to underlying chronic bone disease (osteitis fibrosa cystica). The hypocalcemia may persist despite normal and even elevated PTH levels. Osteitis fibrosa cystica develops due to chronic high levels of PTH leading to increased bone resorption. In addition to hypocalcemia, the patient may also present with hypophosphatemia and hyperkalemia, reflecting the state of high bone turnover. The risk for HBS correlates with the severity of preoperative hyperparathyroidism, bigger size of the excised parathyroid gland, higher age, higher levels of alkaline phosphatase, and the presence of renal failure. Overall, HBS is more prevalent in patients with secondary and tertiary hyperparathyroidism due to chronic renal failure, than in patients with primary hyperparathyroidism [73–76]. The prevalence of HBS in the setting of parathyroidectomy for secondary hyperparathyroidism was reported to be 28% by Goldfarb et al. [77]. Less typically, patients with hyperthyroidism undergoing thyroidectomy can also have underlying high bone turnover due to excess thyroid hormone, and present with HBS [78, 79].

In patients with HBS, the sudden drop in PTH following parathyroidectomy shifts the pendulum from a net increased efflux of calcium from the bones into a net influx of calcium (along with phosphate and magnesium) back into the bones [73]. These patients can experience prolonged periods of postoperative hypocalcemia and are at increased risk of readmission.

The treatment algorithm for hypocalcemia in the setting of HBS follows the same principles for the treatment of postsurgical hypocalcemia previously described in this chapter. However, the surgeon and patient should be prepared for a potentially more drastic and persistent hypocalcemia that can last several months. These patients often demand higher doses of calcium and vitamin D supplementation than for “standard” postoperative hypocalcemia.

As for other etiologies for postoperative hypocalcemia, there are no uniform guidelines for the management of HBS. The goal is to normalize serum calcium levels (along with magnesium and potassium, when indicated) by replenishing the bony calcium deficit and restoring normal bone metabolism.

Conclusion

In many cases, postoperative hypoparathyroidism/hypocalcemia is a preventable complication. Optimal risk stratification, prophylactic supplementation, sound surgical technique, and proper postoperative management are the keys to minimizing morbidity, facilitating early discharge, and preventing readmissions.

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Index

A
Active surveillance, 57, 58
  adoption, 60, 61
  clinical data, 58, 59
  cost effectiveness, 61, 62
  incidence, thyroid cancer, 55, 56
  thyroid cancer care, cost, 56, 57
Afirma Gene Expression Classifier (GEC), 31–34, 37
Afirma Xpression Atlas (XA), 32
Ambulatory endocrine surgery, 271, 272
  potential benefits, 272
Ambulatory parathyroid surgery, 278
Ambulatory surgical centers (ASC), 271
Ambulatory thyroid surgery, 273–278
American Association of Endocrine Surgeons (AAES), 152
American Thyroid Association (ATA), 12
Anaplastic thyroid cancer (ATC), 29, 81, 82
Artifact, 176
Atypia of Undetermined Significance (AUS), 22
Autofluorescence, 211–213
Autonomously functioning thyroid nodules (AFTN), 97

B
Bilateral axillary breast approach (BABA), 260
Bilateral neck exploration (BNE), 108

C
Calcium, 284–289
Clinical framework, 70, 71
Continuous IONM (CIONM), 168
Continuous RLN neuromonitoring (c-IONM), 174

D
Deoxyribonucleic acid (DNA), 26

E
Elastography, 11, 12
Electromyography (EMG), 164
Electrosurgery, 197
Energy devices
  bipolar vessel sealing systems, 198, 199
  challenges, 200
  obstacles, 200
  radiofrequency ablation, 201, 202
  remote access thyroid surgery, 201
  ultrasonic devices, 199, 200
Enzyme-linked immunosorbent assays (ELISA), 128
European Thyroid Association (EU-TIRADS), 12
External branch of the superior laryngeal nerve (EBSLN), 173, 185, 187
  anatomy, 187–189
  injury, 186, 187
  nerve identification, 189
  neuromonitoring technique, 191, 192
  postoperative documentation, 192
  preservation, 190, 191

M. C. Singer, D. J. Terris (eds.), *Innovations in Modern Endocrine Surgery*,
https://doi.org/10.1007/978-3-030-73951-5

F
Familial hypocalciuric hypercalcemia (FHH), 128
Fine needle aspiration (FNA), 116, 117
Follicular thyroid cancers (FTC), 5, 30
Four-dimensional computed tomography (4D-CT), 112, 113

G
Glomerular filtration rate (eGFR), 151

H
Harmonic, 199, 200
Health related quality of life (HRQOL), 258, 261
Hemi-thyroidectomy
  follow up, 77, 78
  historical context, 67–69
  intra-operative evaluation, 73
  postoperative classification, 75
  postoperative evaluation, 74–77
  preoperative classification, 72
  preoperative evaluation, 71, 73
High intensity focused ultrasound (HIFU), 90
Hungry bone syndrome (HBS), 289, 290
Hürthle cell, 30
Hürthle cell adenomas (HCA), 30
Hypercalcemia, 129
Hypocalcemia, 285, 286, 288, 289
Hypoparathyroidism, 283–285, 287

I
Impending neural injury, 176
Indocyanine green (ICG), 207
Intermittent RLN neuromonitoring (i-IONM), 174
Intraoperative nerve monitoring (IONM), 185
  application, 159, 160
Intraoperative neuromonitoring (IONM), *see* Intraoperative nerve monitoring
Intraoperative parathyroid hormone (ioPTH), 108, 131, 219, 220

L
Ligasure, 198–200
Loss of signal (LOS), 174

M
Medullary thyroid cancer (MTC), 31
MicroRNA (miRNA), 27
Minimally invasive video assisted parathyroidectomy (MIVAP), 235, 236
  advantages, 237, 238, 241
  indications, 237, 240, 241
  limits, 238
  technique, 236, 239
Minimally invasive video-assisted thyroidectomy (MIVAT), 238, 245
Misconceptions, 200
Mitogen-activated protein kinase (MAPK), 28
Multi-gland disease (MGD), 108, 109

N
Neoadjuvant therapy, 81, 82, 84
  BRAF-directed therapy, 85, 86
  clinical presentation, 82, 83
  cytotoxic chemotherapy, 84
  external beam radiation, 84
  molecular pathogenesis, 83, 84
New European Surgical Academy (NESA), 258
Nodule selection, 97
Non-recurrent laryngeal nerve (NRLN), 168, 169
Normocalcemic hyperparathyroidism
  clinical features, 140, 141
  diagnostic criteria, 139, 140
  epidemiology, 140
  management, 142
  natural history, 142
  non-specific symptoms, 141
  pathophysiology, 138
  surgical management, 143
Normocalcemic hyperparathyroidism (NCHPT), 125, 138
Normohormonal hyperparathyroidism, 133
  biochemical profile, 127–129
  etiology, 126
  incidence, 126
  intra-operative findings, 130, 131
  localization studies, 130
  long-term success, 132
  presentation, 127

P
Papillary thyroid cancer (PTC), 5, 28, 29, 55, 83

Parathyroid, 107
anatomical imaging modalities, 109–112
choice of imaging algorithm, 117, 118
four-dimensional computed tomography, 112, 113
historical perspectives, 108
imaging, 109
magnetic resonance imaging, 114
nuclear scintigraphy, 114, 115
PET/CT, 116
selective venous sampling, 117
single-photon emission computed tomography, 116
Parathyroid detection, 207
assay characteristics, 220–222
autofluorescence imaging, 211–213
blood samples, 222, 223
detection, 208, 209
final considerations, 229
fluorescence imaging, 214
ICG, 209–211
identification, 208
modern application, 223–226
novel uses, 226–228
Parathyroid hormone (PTH), 219, 283, 286, 287
Parathyroidectomy, 144, 149, 152
indications, 152, 153
intervene, 152
mediated Hypercalcemia, 151
Parathyroid-related hypercalcemia, 149–151
Percutaneous ethanol injection (PEIT), 90
Poorly differentiated thyroid cancer (PDTC), 29
Positron emission tomography/computed tomography (PET/CT), 116
Postoperative calcium management, 283, 284, 287
hypocalcemia, 285
monitoring, 286, 287
risk factors, 284, 285
Postoperative nausea and vomiting (PONV), 277
Post-thyroidectomy neck hematoma (PNH), 274, 275
Primary hyperparathyroidism (PHPT), 107, 125, 137, 138

R
Radioactive iodine (RAI), 67, 69
Radiofrequency ablation (RFA), 97, 197, 201, 202
Randomized control trials (RCT), 278
Recurrent laryngeal nerve, 157, 158, 173, 174, 179, 181
IONM, 158, 159
loss of signal, 164–167
management strategies, 167, 168
negative predictive value, 160
positive predictive value, 160
technique, 160–164
Recurrent laryngeal nerve (RLN), 273, 274
Remote-access thyroid surgery, 259–261

S
Safety, c-IONM, 180
Signal recovery, 179
Single-photon emission computed tomography (SPECT), 115
Society of American Gastrointestinal and Endoscopic Surgeons (SAGES), 200
Staged thyroidectomy, c-IONM, 180
Standardized approach, c-IONM, 174, 175
Superior laryngeal nerve (SLN), 168

T
ThyGeNEXT, 40, 41
ThyGenX/ThyraMIR, 41
Thyroid disease, 3, 4
doppler flow, 10
elastography, 11, 12
image acquisition, 4
risk stratification system, 12, 13, 15, 16
ultrasound characteristics, 5
Thyroid nodules, 45, 89, 90, 101
before ablation, 93
benign nodules, 45
Bethesda III/IV nodules, 43, 44
clinical application, 93, 94
cytological nomenclature, 22–24
evidence supporting, 93
genomics, 26–28
HIFU ablation, 90, 94, 96
indeterminate nodules, 25, 26
molecular testing, 41–43
moving shot technique, 98
papillary thyroid cancer, 28–30
preoperative evaluation, 98
radiofrequency ablation, 97
RFA ablation, 98–100
safety
HIFU ablation, 96, 97
RFA, 100
selection, 91, 93, 97

Thyroid nodules (*Cont.*)
thyroid nodules
cytologically indeterminate results, 31
follicular adenoma, 30
Hürthle cell, 30
medullary thyroid cancer, 31
thyroSeq, 37–40
Thyroid nodules, 21
cytologically indeterminate results, 31
follicular adenoma, 30
Hürthle cell, 30
medullary thyroid cancer, 31
Thyroid surgery, 173, 174, 257
Thyroidectomy vestibular approach (TORTVA), 261, 264, 265
limitations, 264
surgical technique, 262, 263
ThyroSeq, 38
ThyroSeq V2 studies, 38
ThyroSeq v3 studies, 39
Transaxillary, 245, 246
advantages, 250–252
complications, 250
contraindications, 247
disadvantages, 252
indications, 247
patient selection, 246, 247
postoperative, 250
surgical technique, 247, 249, 250
technique, 252, 253

U
Ultrasound (US), 3

V
Visual analogue scale (VAS), 93
Vitamin D, 284, 285, 287, 289
Vocal cord paresis (VCP), 96

W
Well differentiated thyroid carcinoma (WDTC), 81