John B. Hanks
William B. Inabnet III
Editors

Controversies in Thyroid Surgery

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To Dorothy T Hanks (1916–2002), Librarian at the National Library of Medicine, National Institutes of Health from 1959 to 1987. In 1965, she told me when I was in High School that the computer was the way of the future in medicine as she worked with the initial instillation of Medline. Mom seemed to have a knack for being right.

And to our patients who put their trust in us to be up to date in our knowledge and skill and to commit to their optimal care.

John B. Hanks

I dedicate this book to my wife and children—Kathleen, Frances, and William. I am deeply grateful for their unconditional love and support.

William B. Inabnet III

Preface

Plus ca change, plus c'est la meme chose.

Jean Baptiste Alphonse Karr 1849

We both remember our very first thyroid operation as trainees: Dr Hanks with Dr. Sam Wells in 1973 when a first year resident in general surgery at Duke; Dr Inabnet with Blake Cady in 1990 during a visiting surgery rotation at the New England Deaconess Hospital as a 4th year medical student. Over the years, we are grateful to have learned from the very best of our time. We have witnessed the growing importance and relevance of Endocrine Surgery in the training of the General Surgery Resident.

The time tested French proverb, "…..the more things change, the more they stay the same" holds true for Thyroid Surgery. The basic necessity for a successful practice requires extensive knowledge of anatomy, physiology, postoperative care, intraoperative decision making, and skillful surgical techniques. None of these have changed over the last several decades. Yet new technologies, evidence-based decision-making, and interest in quality and outcomes have emerged which impact not just Thyroid Surgery but all of medicine.

So, when we decided to edit this work on "Controversies in Thyroid Surgery," we realized that many topics of current interest impact on the surgical technique we learned all these years ago—for example, the technology of neuromonitoring, robotic or "minimally invasive" approaches, preoperative imaging, and especially ultrasound. Additionally, quality and volume issues that impact referral patterns also impact surgical practice.

We chose each author recognized as an expert in the field and who has made significant national and international contributions to the field of endocrine surgery. Each contributor was assigned to offer their input to areas of thyroid surgery which impact practice patterns today. We are delighted with their response and thoughtfully prepared work. We asked each author to look into the "controversy" generated by the topic. What is the importance, relevance, or cost-effectiveness of the area covered? For example, robotic surgery is impacting general and thoracic surgical procedures; but is it relevant to thyroid surgery?

We hope you will enjoy the thoughts of authors who are well versed to give their opinions on their topics. We have had a ball putting it together.

Our sincere thanks go to Tracy Marton, our Editor at Springer, who stuck with us during the preparation of the work. She is a thoughtful and thorough partner, with the patience of a Saint. To her, we owe a great debt.

Charlottesville, VA, USA — John B. Hanks, M.D., F.A.C.S.
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Part I

General Topics

Controversies in the Management of Nodular Thyroid Disease

1

Judy Jin and Christopher R. McHenry

Introduction

In general, the evaluation and management of nontoxic nodular thyroid disease are straightforward. However, there remain several areas of controversy where differences in opinion exist regarding the nuances in evaluation and management of patients with a thyroid nodule and a specific fine needle aspiration biopsy (FNAB) result. Some of the controversial issues include: the appropriate evaluation and management of patients with a thyroid nodule and an FNAB categorized as atypia/follicular lesion of undetermined significance (AFLUS), the intraoperative management and extent of thyroidectomy for patients with an FNAB suspicious for papillary thyroid cancer (PTC) and the extent of thyroidectomy for patients with benign nodular thyroid disease with an established indication for surgical therapy. In this chapter, we will review the evaluation and management of nontoxic nodular thyroid disease with emphasis on areas of controversy.

Epidemiology

Thyroid nodules are common. The prevalence of thyroid nodules varies with the study population as well as the method used for detection. In the Framingham study performed during the era when physical examination was the primary method of diagnosis, a 4.2 % prevalence was reported, 6.4 % in women and 1.5 % in men [1]. However, the prevalence in autopsy series and studies examining results from neck ultrasound can be as high as 67 % [1–3]. Thyroid nodules are more common in women, and the incidence increases with age. Fortunately, 95 % of thyroid nodules are benign.

In the recent years, an increased number of thyroid nodules have been discovered incidentally on ultrasound (US), computed tomography (CT), magnetic resonance imaging (MRI), and positron emission tomography (PET) performed for reasons unrelated to the thyroid gland. The rate of thyroid incidentalomas discovered on imaging studies varies from 20 to 30 % [4]. An incidental thyroid nodule with focal FDG uptake on PET imaging is of the most concern, because of a 35 % risk of malignancy [5].

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Evaluation

In general, a workup is initiated for thyroid nodules ≥1 cm in size. Nodules <1 cm are evaluated in patients with a prior history of head or neck irradiation, a family history of thyroid cancer in a first degree relative, or abnormal sonographic features. A thyroid nodule identified by a focal area of FDG uptake on ^{18}FDG-PET imaging should be evaluated even when it's less than one centimeter because approximately one-third of these are malignant.

The evaluation of a patient with a thyroid nodule should consist of a history and physical exam, a screening serum TSH level, a US exam of the neck, and an FNAB. Molecular testing of the fine needle aspirate may supplement this approach, particularly in a patient with an indeterminate FNAB. Currently, gene expression profiling may exclude cancer by determining which nodules have a benign RNA expression profile, while gene mutation panels may try to establish a diagnosis of cancer by identifying DNA alterations [6, 7].

The evaluation of a patient with a thyroid nodule begins with a complete history and physical examination. Patients are asked about symptoms of hyperthyroidism and hypothyroidism, dysphagia, dyspnea when supine, coughing or choking spells, hoarseness or change in voice, neck pain, obstructive sleep apnea, and rapid nodule growth. With the increasing rate of thyroid incidentalomas detected on imaging studies, patients may not have any signs or symptoms at presentation.

In addition, patients are asked about a prior history of head or neck irradiation and a family history of thyroid cancer, other familial syndromes, or endocrinopathies. Patients with a thyroid nodule and a history of head or neck irradiation have an approximate 40 % incidence of carcinoma, and the cancer may be found outside of the index nodule [8]. Familial nonmedullary thyroid cancer, defined as differentiated thyroid cancer occurring in two or more first degree relatives, accounts for 5 % of all thyroid cancers. Thyroid cancer may also occur as part of other familial syndromes including multiple endocrine neoplasia type IIA and type IIB, familial adenomatous polyposis, Gardner's syndrome, Cowden's disease, Carney's disease, and Werner's syndrome.

Physical examination should include an evaluation of the size and character of the index nodule, the presence of neck tenderness that can occur in patients with thyroiditis, and the presence of any other thyroid nodules. The presence of substernal extension should be determined, and the trachea should be evaluated for displacement. The rest of the neck should be evaluated for associated cervical or supraclavicular lymphadenopathy. At minimum, laryngoscopy should be performed for patients with hoarseness or a change in voice. Findings on physical examination that are suggestive of cancer include a firm, fixed nodule, a paralyzed vocal cord, and cervical lymphad enopathy.

A screening serum TSH level is obtained in all patients. The majority of the patients who present for evaluation of nodular thyroid disease are euthyroid, and no additional thyroid function tests are necessary. In patients with a thyroid nodule and a low serum TSH level, a free T4 and free T3 level are obtained, and FNAB is reserved for a hypofunctioning nodule identified on an iodine-123 thyroid scan. The risk of malignancy for a hyperfunctioning nodule is <1 %, and antithyroid drug therapy, radioiodine, and thyroid lobectomy are all options for treatment.

US is the best imaging modality for evaluation of the thyroid gland. Once a thyroid nodule has been detected, either on physical exam or by other imaging studies, all patients should undergo a US examination of the neck. This includes a survey of the thyroid gland and an assessment of the central and lateral compartments of the neck for abnormal lymphadenopathy. US is also used for routine surveillance of patients with a familial cancer syndrome known to be associated with an increased risk of differentiated thyroid cancer (DTC). When a thyroid nodule is identified, it should be evaluated for specific sonographic characteristics including hypoechogenicity; a shape that is taller than wide, irregular, or infiltrative borders; an absent halo; increased intranodular vascularity; and microcalcifications, all of which have been associated with increased risk

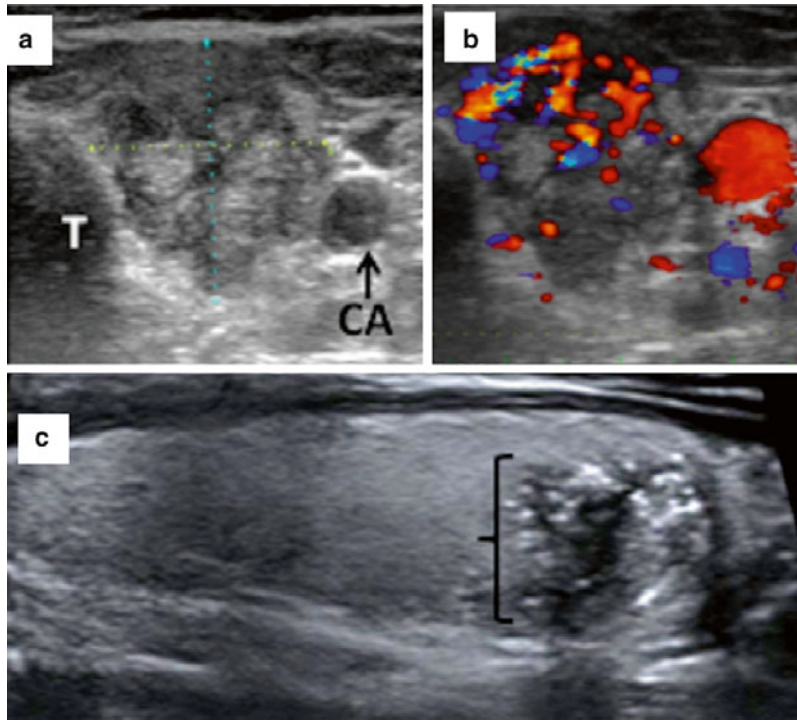

Fig. 1.1 Sonographic features raising suspicion for cancer: (**a**) a hypoechoic thyroid nodule with irregular borders that is taller than wide (**b**) increased intranodular vascularity, and (**c**) microcalcification. *T* trachea, *CA* carotid artery

for thyroid cancer [9–14] (Fig. 1.1). Increasing nodule size has not consistently been linked with cancer [15]. In the management of goiterous disease, when the lower pole of the thyroid lobe cannot be visualized with patient's neck in hyperextension, a neck and chest CT may be considered as the potential for substernal component is high.

An abnormal cervical lymph node seen is more rounded in appearance on US examination, with the absence of the hyperechoic stripe representing the vascular pedicle. The presence of cystic change and microcalcifications is also indicative of an abnormal lymph node. Figure 1.2 is a screening US examination from a patient with familial adenomatous polyposis demonstrating a sonographically normal thyroid gland and an abnormal lymph node in the central compartment of the neck with a rounded contour and microcalcification. An FNAB of the lymph node revealed papillary cancer. Figure 1.3 shows a US image from a patient with a solitary 3.2 cm left thyroid nodule who had an abnormal 2 cm contralateral, level III lymph node detected, and FNAB revealed metastatic papillary cancer. These examples underscore the importance of routine evaluation of the central and lateral compartments of the neck for abnormal lymph nodes in patients with nodular thyroid disease.

The American Thyroid Association Guidelines (ATA) [16], guidelines for patients with thyroid nodules and thyroid cancer, recommend FNAB for a thyroid nodule greater than one centimeter, with the exception of a pure cystic nodule, which comprise <2 % of thyroid nodules. FNAB is also recommended for a nodule less than 1 cm with abnormal sonographic features, PET positivity or in a patient with a family history of PTC, a personal history of treated thyroid cancer or a history of radiation exposure. FNAB with palpation has been the standard method of biopsy, while US-guided FNAB has been preferentially used for nonpalpable nodules, for nondiagnostic FNAB performed with palpation, and for

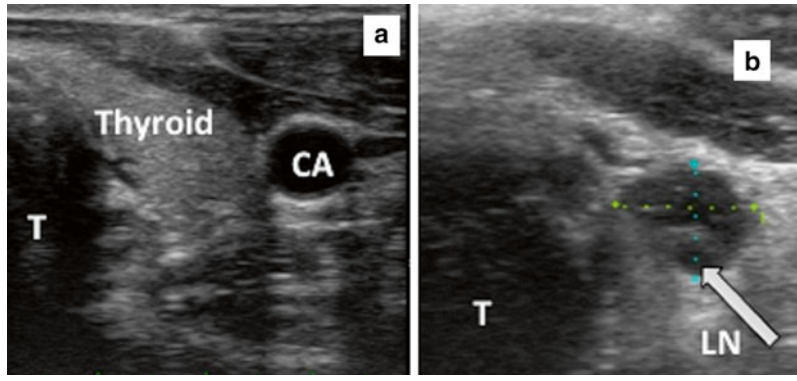

Fig. 1.2 Screening thyroid US in a patient with familial adenomatous polyposis syndrome: (**a**) normal-appearing thyroid lobe without any nodules (**b**) central neck lymph node that is round and contained calcification. *T* trachea, *CA* carotid artery, *LN* lymph node

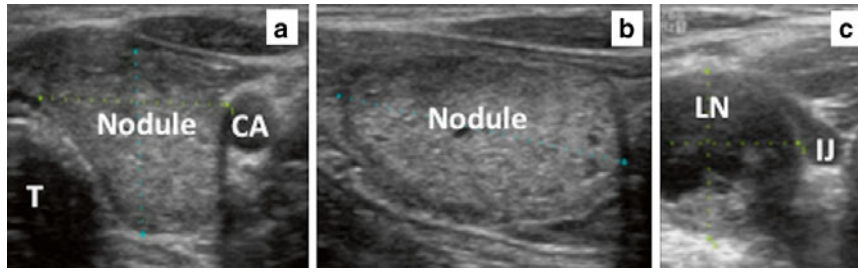

Fig. 1.3 A 27-year-old patient with a solitary left toxic nodule (**a**) and (**b**) a partially cystic contralateral level III lymph node. Biopsy consistent with metastatic papillary thyroid cancer, *T* trachea, *CA* carotid artery, *IJ* internal jugular vein, *LN* lymph node

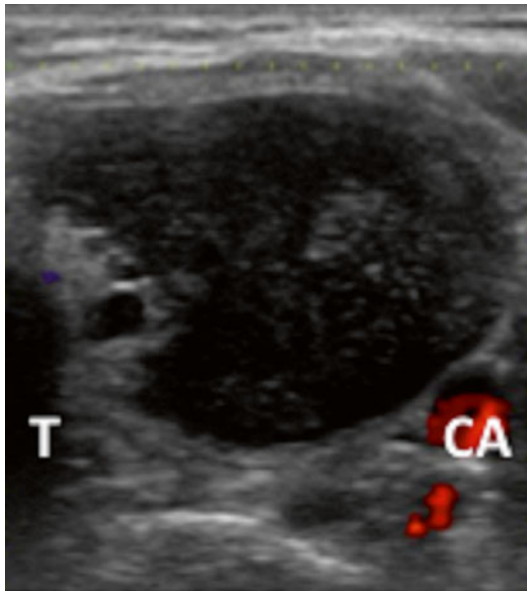

Fig. 1.4 Predominately cystic thyroid nodule where US guidance is necessary to biopsy the solid component

predominately cystic nodules to ensure biopsy of the solid component. However, with the increasing availability of US, some have recommended that all thyroid nodules be biopsied with US guidance [17]. Ultrasound is helpful in guiding the biopsy needle into the solid component of a mixed solid/cystic nodule and in the suspicious areas of a solid nodule (Fig. 1.4).

Management

The National Cancer Institute (NCI) hosted the "Thyroid Fine Needle Aspiration State of the Science Conference" in 2007, and from this conference, The Bethesda System for Reporting Thyroid Cytopathology (BSRTC) was developed [18]. The BSRTC was modeled after the Bethesda System for reporting cervical cytology and is composed of six cytologic categories, each with

an estimated risk of malignancy and distinct recommendations for management. It was initiated in order to help promote more consistent management of patients with nodular thyroid disease. This was intended to be a flexible framework that could be modified to suit the needs of the particular cytopathology lab and the specific patient. However, it has also produced some unintended consequences, which have resulted in differences in opinion regarding interpretation and management. In the following section, we will describe each of the cytologic categories, their clinical implications, treatment options, and describe some of the existing controversy.

Bethesda I

The first cytologic category is "nondiagnostic." A thyroid FNAB specimen is classified as nondiagnostic when the criteria for specimen adequacy have not been met. In order for a specimen to be satisfactory for interpretation, at least six groups of 10 or more of well-preserved follicular cells should be present on at least 2 aspirates. A nondiagnostic FNAB should be repeated, and in 50–88 % of cases, an adequate specimen will be obtained. The ATA guidelines recommend that an iodine-123 thyroid scan can be obtained in a patient with a low normal serum TSH level to distinguish a hypofunctioning nodule, which is more likely to be malignant from a hyperfunctioning nodule, one that is rarely malignant and can be treated without thyroidectomy.

A nondiagnostic sample should be expected when a pure cystic nodule is biopsied; hemosiderin-laden macrophages and cellular debris with or without colloid are all that is usually retrieved. When correlated with US findings and clinical examination, a nondiagnostic result from a pure cystic nodule may be considered benign, and the patient can be followed clinically. This is in contrast to the patient with a complex cystic-solid nodule (Fig. 1.4), where repeat biopsy of the solid component of the complex nodule is imperative.

Surgical therapy is recommended for patients with a persistent nondiagnostic FNAB due to an approximate 8 % risk of malignancy [19]. Operative management consists of a thyroid lobectomy, isthmusectomy, and frozen section exam (FSE). A total thyroidectomy is performed for a frozen section diagnosis of cancer.

Bethesda II

The second cytologic category is "benign," accounting for approximately 60 % of all FNAB results. The false negative rate is approximately 2–3 % [20]. Patients can be followed clinically with a history, physical examination, serum TSH level, and surveillance ultrasound. Repeat FNAB is recommended for nodule growth to exclude a rare false negative result. Thyroidectomy is indicated for compressive symptoms, radiographic evidence of tracheal, esophageal, or major vascular impingement, substernal extension, development of thyrotoxicosis, and cosmetic concerns.

One area of controversy is the appropriate extent of thyroidectomy for benign nodular thyroid disease. Traditionally, a subtotal thyroidectomy was the standard procedure performed for benign nodular thyroid disease. The rationale was to reduce the likelihood of recurrent laryngeal nerve injury and hypoparathyroidism and leave enough thyroid tissue behind to maintain euthyroidism. However, recurrence rates between 5 and 43 % were noted after a mean follow up of 9–10 years [21–24]. The high recurrence rates have led others to recommend total thyroidectomy for benign nodular thyroid disease [25]. Most of these data came from an era where thyroid US was not routinely available for assessment and management of thyroid nodular disease. Currently, US can provide a detailed anatomy of the remainder of the thyroid gland in addition to the index nodule. Our approach is to perform a thyroid lobectomy and isthmusectomy when contralateral disease is excluded by preoperative US exam and intraoperative palpation. This is associated with a 2 % recurrence rate and maintenance of euthyroidism in 73 % of patients [26]. When there is significant contralateral disease, defined by a nodule $\geq$1 cm, a total thyroidectomy is performed, especially in younger patients who are at increased risk of recurrence.

Bethesda III

The third cytologic category is AFLUS. This is a new category used for heterogeneous cytologic findings including variable degrees of nuclear or architectural atypia that precludes a definitive diagnosis of benign or neoplastic disease. AFLUS was projected to account for less than 7 % of all FNAB specimens; however, the reported rates have varied from 3 to 47 % [27–31]. The estimated risk of malignancy by the State of the Science Conference at the NCI was 5–15 %; however, rates of 6–48 % [31, 32] have subsequently been reported after the introduction of AFLUS into clinical practice. The variability in the incidence of AFLUS may be from either "undercalling" a specimen that would have been previously classified as a follicular or Hurthle cell neoplasm or suspicious for papillary cancer or "overcalling" a specimen that previously would have been classified as benign. Knowing the institutional experience is important when advising patients regarding treatment. It is expected that the incidence of AUS will decrease with increased experience.

The current recommendation for an FNAB with AFLUS is to repeat the FNAB in 3–6 months. However, performing a repeat FNAB sooner has not been found to affect the cytologic interpretation [33]. In general, an interval waiting of at least 4 weeks should be performed to minimize atypia associated with inflammation, and a repeat FNAB can be definitive in 2/3 of patients [34, 35]. Due to the heterogeneity of the AFLUS group, some clinicians have proposed further stratification of this category to provide additional guidance for clinical management. Specimens containing a moderate or large amount of thin colloid and nuclear atypia without nuclear inclusions are more likely to be benign [30]. On the other hand, a specimen containing micro follicles [35] with or without associated cellular atypia has been shown to have a rate of malignancy of 20–30 % [36]. When marked nuclear atypia (prominent nucleoli, enlarged irregularly shaped nuclei with irregular chromatin, more than rare nuclear inclusions and grooves) is present, the likelihood of malignancy is high, approximately 50 %. Because of the higher risk of cancer associated with this subcategory, multiple institutions have independently separated this into its own separate cytologic category [32, 37]. It has been labeled as "atypical epithelial cells, cannot exclude papillary carcinoma" and has a reported cancer risk of 40–50 % [38].

Despite the recommendation to perform a repeat FNAB in patients with an initial AFLUS result, up to 65 % of patients are operated on without a second biopsy [28, 35]. In one study it was reported that patients with AFLUS and more than rare nuclear inclusions or nuclear grooves had a higher risk for cancer, and as a result, it was recommended to forego repeat FNAB and proceed with thyroidectomy [30]. There is inherent selection bias when particular patients are chosen to undergo surgery rather than repeat FNAB. When patients have an FNAB classified as AFLUS, other clinical, cytologic, or molecular features are taken into consideration beyond the suggestions put forth by the Bethesda System. These include a personal history of head and neck radiation, family history of thyroid cancer, US or clinical features that are worrisome for cancer, additional thyroid disease other than the index nodule and the results of oncogene testing and/or gene expression profiling. Thyroid lobectomy, isthmusectomy, and FSE are recommended for patients with nodular thyroid disease limited to one lobe. FSE is of value in establishing a diagnosis of papillary cancer. It has a high specificity and positive predictive value in patients with AFLUS. As a result, a malignant FSE diagnosis can be used to reliably recommend proceeding with definitive total thyroidectomy.

Bethesda IV

The fourth cytologic category is suspicious for follicular neoplasm or follicular neoplasm (SFN/FN), it includes both follicular and Hurthle cell neoplasm. This category is characterized by a cellular aspirate with a predominance of follicular or Hurthle cells (comprising >75 % of the

cells) in sheets, micro follicles, or a trabecular pattern with scant or absent colloid. Nuclear atypia/pleomorphism and mitoses are usually uncommon. Prior to the introduction of the BSRTC, an FNAB consistent with a follicular or Hurthle cell neoplasm constituted approximately 20 % of all FNAB results. Chen et al. [34] demonstrated that FNAB results consistent with a follicular or Hurthle cell neoplasm decreased significantly following the introduction of the BSRTC. This is secondary to specimens that are now being classified as AFLUS. The overall cancer risk associated with an FNAB that is consistent with a follicular or Hurthle cell neoplasm is approximately 20–30 %. The spectrum of potential final pathologic diagnoses in a patient with a follicular neoplasm includes follicular adenoma, adenomatous hyperplasia, follicular carcinoma, follicular variant of PTC, and classical PTC. The spectrum of potential final pathologic diagnoses in a patient with a Hurthle cell neoplasm includes Hurthle cell adenoma, Hurthle cell nodule, thyroiditis, and Hurthle cell carcinoma.

Additional testing may be useful in patients with an FNAB SFN/FN. An iodine-123 thyroid scan is obtained in a patient with an FNAB classified as a follicular neoplasm or suspicious for a follicular neoplasm and a low normal serum TSH level to distinguish a hypofunctioning nodule, which is more likely to be malignant from a hyperfunctioning nodule, which is rarely malignant and does not necessarily require thyroidectomy. Gene expression profiling is being used for patients with an FNAB categorized as AFLUS or SFN/FN. However, there are no established guidelines, it is expensive and labor intensive, and its cost-effectiveness has yet to be elucidated. A sensitivity of 90 %, a specificity of 53 % and 49 %, and a negative predictive value of 95 and 94 %, respectively, have been reported [39]. The overall 5–15 % false negative rate that has been reported with the gene classifier and the limited number of validation studies makes it difficult for some patients to forego operative therapy when they can't be assured that they don't have cancer. Genetic testing for oncogene mutations may be of value in patients with AFLUS or SFN/FN when gene expression profiling is suspicious for malignancy, which has a false positive of 62 and 63 %, respectively [37].

All patients with a Hurthle cell neoplasm, a follicular neoplasm with a normal or high serum TSH level, or when the neoplasm is hypofunctioning on thyroid scintigraphy should undergo thyroidectomy. In most patients, it is the presence or absence of capsular or vascular invasion that distinguishes a malignant follicular or Hurthle cell neoplasm from a benign follicular or Hurthle cell neoplasm. At the time of operation, a thyroid lobectomy and isthmusectomy is the standard operation in the absence of extrathyroidal tumor spread, lymph node metastases, and nodular disease in the opposite lobe. Intraoperative frozen section is not performed because it is rarely of value in identifying capsular or vascular invasion. A completion thyroidectomy is recommended for patients with a final pathologic diagnosis of cancer.

Bethesda V

The fifth cytologic category is suspicious for PTC. This is a category used when some but not all of the cytologic criteria of PTC are present in combination with otherwise benign features. It accounts for approximately 5 % of all FNAB results. The malignancy rate for this category is approximately 60–75 %. Molecular testing for oncogene mutations associated with PTC may be of value in patients with a thyroid nodule and an FNAB suspicious for PTC when there is no other indication for definitive total thyroidectomy. Identification of an oncogene mutation has been reported to be associated with an 88-95 % rate of malignancy and thus warrants proceeding with a definitive total thyroidectomy [40].

In the absence of an oncogene mutation, the operative management of a patient with a thyroid nodule and an FNAB suspicious for PTC can be a therapeutic dilemma and is a subject of controversy. There is no consensus on what constitutes the appropriate intraoperative management of a patient with a thyroid nodule and an FNAB suspicious for PTC. This is in part due to the variable rates of malignancy reported in the literature,

which range from 40 to 82 % [41]. Because of the high rates of PTC, some authors recommend proceeding with total thyroidectomy in all patients with an FNAB suspicious for PTC. It has also been suggested that a total thyroidectomy is a more cost-effective approach [42]. Mittendorf et al [43] reported that FSE altered the decision-making regarding extent of thyroidectomy in 56 % of patients with an FNAB suspicious for PTC. As a result, in patients with nodular disease limited to one lobe of the thyroid gland that is confirmed to be benign on FSE, limiting thyroid resection to a lobectomy and isthmusectomy is a reasonable alternative.

Bethesda VI

The sixth and final category in the BSTRC is the malignant group. It accounts for approximately 5 % of all FNAB results. An FNAB that is malignant has a false positive rate of only 1–2 %. As a result, patients with a malignant FNAB should undergo a definitive total thyroidectomy. It is important to remember that a careful survey of the cervical lymph nodes should be done to look for potential metastatic disease. Patients with macroscopic lymph node metastases in the central compartment of the neck should undergo a concomitant central compartment neck dissection, and patients with lymph node metastases in the lateral neck should undergo a lateral neck dissection.

Conclusion

History and physical exam, a screening serum TSH level, and ultrasound examination of the neck and FNAB constitute the mainstay in evaluation of a patient with a thyroid nodule. Iodine-123 thyroid scintigraphy is used selectively in patients with a persistently nondiagnostic or an SFN/FN FNAB. Thyroid lobectomy and isthmusectomy with intraoperative FSE is the standard operation for a patient with nodular thyroid disease and an FNAB that is persistently nondiagnostic, AFLUS or suspicious for PTC. Thyroid lobectomy and isthmusectomy without FSE is the standard operation for patients with nodular thyroid disease and an FNAB with SFN/FN; however, clinical factors and the results of molecular testing may lead to performance of definitive total thyroidectomy. A definitive total thyroidectomy is performed for a patient when FNAB is malignant.

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The Use of Ultrasound in the Management of Thyroid Disorders

2

Mira Milas, Maisie Shindo, and Elena K. Korngold

Introduction

Ultrasound is the best imaging modality applied to the modern evaluation of thyroid disease. There is very little controversy about this role. Ultrasound provides details about the anatomical structure and pathology of the thyroid that are unparalleled by other radiologic modalities and offers the most versatility for conducting clinical care of patients with thyroid disease. Many clinicians, in fact, have described the fundamental role of ultrasound in patient care by saying "it's just like a stethoscope." The challenges, and perhaps controversies, in current application of ultrasound for thyroid disorders can be categorized into the following three themes: the role of different specialties in performing thyroid ultrasound, standardization of ultrasound reporting, and pattern recognition for optimal disease assessment and treatment. Unifying these issues is the theme of education. This chapter explores these challenging topics with the goal of providing up-to-date resources and tools to enable optimal use of thyroid ultrasound and with the hope of highlighting the best of thyroid ultrasound.

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Specialty Involvement in Thyroid Ultrasound: Who, Why, How, Where, When

It may be helpful to consider how ultrasound became an integral part of clinical assessment of the thyroid in current patient management [1–7]. Historically, real-time, gray-scale B-mode ultrasound was available as early as 1980 and was almost exclusively in the domain of radiologists. More than a decade later, ultrasound in the United States began to be used at the patient's bedside by treating clinicians, such as in trauma and critical care, and also by endocrinologists for thyroid disease. The early hope was that ultrasound by itself would distinguish between benign and malignant thyroid nodules, but this has so far not been the case. Instead, fine-needle aspiration biopsy (FNA) had had more success in this regard

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and was a fledgling concept perhaps, even earlier than ultrasound, in the mid-1970s. Temporarily, this caused clinicians to focus more on information from thyroid nodule FNA than information they could obtain by "hands-on" evaluation with ultrasound. Thyroid FNA in the early phases of its clinical use was performed by nodule palpation and without ultrasound guidance. It was not immediately recognized how complementary these interventions were in achieving a diagnosis. Even in a publication from 1997, rightfully extolling the virtues of FNA as a method to avoid diagnostic thyroidectomy for benign nodules, it is interesting to observe that none of the FNAs were ultrasound guided [6].

Practical advances in technology improved the quality and accessibility of thyroid ultrasound. Multiple manufacturers made ultrasound machines available in versatile configurations, including in more portable form. Transducers came in high-resolution (7.5–10 MHz) linear and curvilinear arrays that were optimal for the fine imaging required of delicate thyroid and other neck structures. When good quality ultrasound equipment was available for less than $20,000, instead of hundreds of thousands of dollars, clinicians could feasibly acquire it for their clinics. This combination of factors significantly increased the momentum of "clinician-performed ultrasound." By 2004, the era of thyroid ultrasound received a resounding endorsement. In an editorial featured in the high-impact journal Thyroid (affiliated with the American Thyroid Association), endocrinologist and thyroid ultrasound pioneer Jack Baskin simply exhorted: "Thyroid Ultrasound: Just Do It" [1].

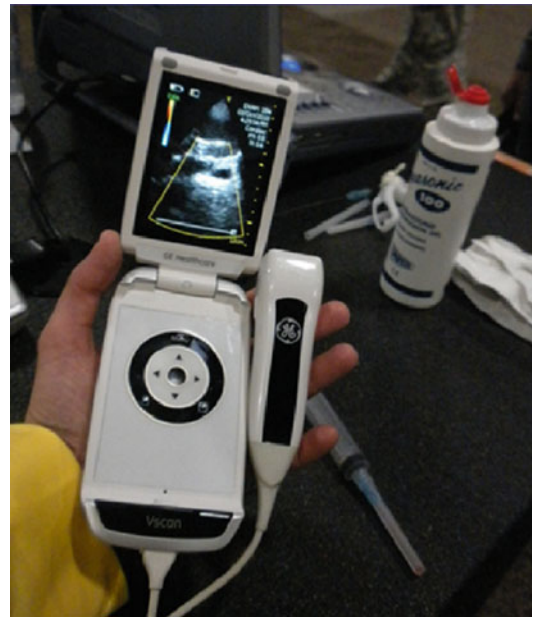


Fig. 2.1 Ultrasound equipment has evolved to become smaller, portable, yet with excellent image quality, making it available to many physicians in the care of their patients

Who Performs Thyroid Ultrasound

By 2014, 10 years following Baskin's editorial, thyroid ultrasound can be performed using pocket-sized ultrasound devices (Fig. 2.1) and is beginning to expand into primary care and emergency medicine patient encounters [8, 9]. So who can or should, therefore, perform thyroid ultrasound? By sequential historical order (from earliest to most recent), the answer to this question is radiologists, sonography technologists ("sonographers"), endocrinologists, surgeons, pathologists, emergency medicine physicians, primary care physicians, and now residents and medical students. The conduct and interpretation of thyroid ultrasound is a learned skill. The talent or intrinsic ability for this skill is not specialty based, and educational venues to learn thyroid ultrasound are usually multidisciplinary [10–12].

Several critical factors are valuable to keep in mind, when considering who will perform thyroid ultrasound: the patient and their clinical need, the extent of ultrasound expertise to address this need, the availability of ultrasound equipment and specialists, and the ease of interdisciplinary communication. Each clinical setting, hospital, university, or other medical setting will have a unique answer as to how these factors are considered and goals are achieved. The following examples illustrate the variability of practice patterns nationally. In a stand-alone private practice setting, with exclusive focus on thyroidology, an endocrinologist performs diagnostic, interventional, and problem-focused ultrasound. In a university

setting, a radiology department performs all of these functions, and no clinician at a "point-of-care" access has the equipment or skill for ultrasound. In a multidisciplinary rural clinic, a surgeon has ultrasound certification and performs thyroid ultrasound and FNA, as the nearest radiology center is a 2-h drive away. In a family medicine clinic, a physician who performs a neck physical exam on an obese patient is unsure whether a thyroid nodule was palpated; the physician uses a portable ultrasound to image the thyroid and sees that it is normal in size and texture, thus clarifying the physical exam finding in real time, at the original clinic visit, and without added cost.

Recent publications have outlined the benefits of particular specialists performing thyroid ultrasound [13–20]. They have also identified that the knowledge and exposure to thyroid ultrasound and its optimal use are still not universal, regardless of specialty [20, 21]. The authors of this chapter were purposefully chosen to represent the disciplines at our university (surgery, otolaryngology, and radiology) which currently engage in thyroid ultrasound for patient care. Each individual practitioner will have a view, based on their experience and philosophy, which informs the use of ultrasound. From a surgical perspective, the benefit gained by a surgeon who will subsequently expose the thyroid during operation, from imaging the thyroid themselves and understanding anatomical findings ahead of surgery, is exceptionally useful. In general and endocrine surgery, ultrasound skill is learned early on by exposure to imaging in many clinical situations: the chest and abdomen in trauma; vascular access and cardiac applications in critical care; peripheral vascular disease evaluation; the liver, pancreas, and adrenal glands in the context of managing surgical oncology patients or hepatobiliary cancers; and of course head and neck disease. In the otolaryngology field, ultrasound is a very important diagnostic tool to evaluate a broad spectrum of head and neck malignancies, as well as benign disorders. From a radiology perspective, ultrasound is a fundamental, specialty-defining component that can and should be preserved in this capacity, for application in thyroid/neck and other small-parts ultrasound, as well as a diagnostic and interventional technique in essentially every other organ system. As more specialists begin to perform their own ultrasound, it is critical that the experience of radiologists and ultrasound technicians as well as training of radiology residents not be compromised, since the majority of providers will still need to send patients to radiology for ultrasound studies. From all perspectives exposed to the training of residents and medical students, exposure to ultrasound is essential for knowledge and skill acquisition.

Communication is also essential to optimal medical care regardless of who is performing thyroid ultrasound. Not all specialists will have access to clinical information about the patient which may be important to inform decision-making relevant to thyroid ultrasound or FNA. This is principally a limitation of our current medical systems even when electronic health records (EHR) are available. It can also be a limitation of knowledge in some situations, where the specialist technically performing the ultrasound exam may not be as familiar with the most recent recommendations for thyroid disease management. For example, the advice given in an ultrasound report to biopsy a thyroid nodule may not be appropriate if the patient is hyperthyroid, but this clinical fact may not have been available to the individual performing the ultrasound. The sections further in this chapter that address ultrasound pattern recognition and reporting will expand on this conundrum. The most effective solution to challenges of this kind, and one that keeps the patient in focus, is collegial and open communication among various clinicians involved with the care of the patient. Whether this occurs by something as simple as a phone call, sharing of clinical records, multidisciplinary discussion, direct partnership as an ultrasound is performed, or more advanced EHR functions, communication is irreplaceable to achieve the best patient care result.

Why and How to Perform Thyroid Ultrasound

The indications for performing thyroid ultrasound and the unique information it provides are listed in Table 2.1 [22–28]. The clinical reasons to perform ultrasound can be categorized as having a diagnostic versus interventional role. Furthermore, in the context of thyroid disease diagnosis, the ultrasound can be intended for comprehensive versus problem-focused evaluation. The terms "point-of-care," "clinician-performed ultrasound," and "surgeon-performed ultrasound" have also entered the professional vocabulary primarily as a means to convey ultrasound being performed at the penultimate point of clinical decision-making, between the patient and the one physician ultimately responsible for their care. These terms are unlikely to disappear. They make logical sense from the perspective of primary care providers or ambulatory clinic-based physicians but can evoke unintended juxtaposition to care given within a traditional radiology department structure. To minimize controversy in this regard, professional societies have articulated policy statements, have worked together to offer ultrasound certification under accreditation acceptable to several specialties, and provide ongoing, collaborative educational opportunities [22–28]. It is the responsibility of the physicians at any particular clinic or hospital setting to decide ultimately where expertise resides and how they will deliver the best care needed for all indications of thyroid ultrasound application: comprehensive diagnostic, problem-focused diagnostic, and interventional.

Indications specifically as they relate to thyroid cancer-related ultrasound have been described extensively [22–30]. The theme is highlighted here to point out that the benefits to patient care are so beneficial that, instead of controversy, there has been a preponderance of thoughtful agreement on best practices. All patients diagnosed with thyroid cancer need a comprehensive diagnostic thyroid ultrasound that specifically evaluates for cervical metastases prior to any initial surgery [18, 29, 30]. The challenge, or controversy, may be to discern why such a basic clinical principle has not been assimilated universally in physician practices, as can be observed by experience even 10 years after it was originally advocated. Similar challenges have been reported with the dissemination and adaptation of clinical practice guidelines in general [31–34]. Contemporary papers from the Association of Ultrasound in Medicine (AIUM 2014) and the American Thyroid Association (ATA January 2015) have reemphasized the need and benefits

Table 2.1 Indication for information gained from thyroid ultrasound

Indications for thyroid ultrasound
• Clarification of exam finding in neck/thyroid
• Accurate diagnosis of initial thyroid disease
• Characterization of thyroid nodules (size, composition, vascularity, etc)
• Improvement of targeting accuracy of FNA
• Visual guidance for interventional therapy (cyst drainage, alcohol ablation)
• Facilitation of objective monitoring of therapy
• Identification of recurrent/persistent cancer
• Evaluation of cervical lymphadenopathy or metastases
• Optimization of surgical planning based on additional findings (signs of local invasion, substernal extent of thyroid enlargement, contralateral thyroid lobe disease, tracheal deviation, gland vascularity)
• Assessment of vocal function by laryngeal ultrasound
• Identification of co-existing pathology (parathyroid disease, other head and neck malignancies)
• Intraoperative evaluation (confirmation of findings, optimal placement of incisions, image guidance to detect pathology if unclear)
• Education

of preoperative ultrasound imaging for thyroid cancer patients [28, 30].

How ultrasound is conducted varies depending on the indication and the specialist performing the study. A number of excellent resources illustrate step-by-step techniques for both diagnostic and interventional thyroid ultrasound applications [28, 35–38]. It is valuable to consider them carefully and modify existing practices as needed. A brief overview is provided here for general appreciation of the process. A good starting point in the conduct of ultrasound relies on the verification of three key "P"s: *p*atient identification being entered for documentation, the *p*robe of choice being selected for imaging (since several different probes may be attached to the ultrasound), and that the ideal machine *p*reset of image quality settings is optimized for the thyroid. The patient should be positioned comfortably on the examining table, with excellent exposure of the relevant regions of the neck. The step-by-step conduct of performing the ultrasound should proceed in the same sequence each time, as this facilitates being comprehensive and obtaining consistent images. Thus, for example, a sequence can be to image the isthmus transversely, then the right lobe in both transverse and longitudinal views, then the left lobe likewise, then move towards characterization of any thyroid pathology (nodules), and conclude with a survey of lymph nodes in the central and lateral necks. A decision can be made whether the patient meets criteria for FNA and when and how to perform this. While the details of this procedure and decision-making are beyond the goals of this chapter, it is important to emphasize a philosophical concept: an FNA of a thyroid nodule, for example, should be performed only when truly indicated and when the result will change subsequent decision-making. Many nodules might meet criteria for FNA by their individual appearance, but FNA may not be needed for the treatment of the patient as a whole. A report (see subsequent section) is ideally written at the time of imaging and includes key features that will describe the normal or abnormal pathology. The ultrasound study should then be saved into the medical record or hospital imaging repository. A practical guide to initial set-up of an office-based ultrasound practice also provides a sophisticated, illustrated example of a thyroid ultrasound report and is highlighted in the section on Standardization of Ultrasound Reporting below.

As in any technical field, practitioners will have certain preferences based on data, experience, tradition, and comfort level. For example, the needle direction used to perform thyroid nodule FNA can be parallel or perpendicular to the ultrasound transducer footprint, based on the target and the preference of the user. Practitioners may choose different transducers for procedures based on approach or size of the acoustic window. For example, linear probes provide exceptional imaging quality and a wider field of view. Depending on the location of a nodule or lymph node, as well as the bulk size of the linear transducer, needle guidance may be more challenging during FNA. In contrast, small curved probes (which are not provided by all ultrasound manufacturers) are excellent FNA guides, especially since they can be positioned better near the sternal notch. The image quality of these small curved probes is not as excellent in providing nodule details.

Such variations in how to conduct the sequence of an ultrasound exam, or which probe is preferred for FNA guidance, are unlikely to impact patient care by experienced ultrasound users. However, there are variations that do influence diagnostic accuracy, and controversy has resided in how best to bring attention and resolution to these issues. An example is that thyroid ultrasound is often executed in a very literal fashion, describing the findings confined to the right and left thyroid lobes and isthmus. This means that the ultrasound machine setting may be placed at a magnification that excludes adjacent anatomy from view. The AIUM has recently advised that even a basic cervical lymph node screening (instead of detailed mapping of metastases) can be included with an initial diagnostic thyroid ultrasound [28]. For some practitioners, this may mean adjusting the settings of the ultrasound machine to acquire images from deeper regions and then physically passing the transducer probe to cover a wider neck surface. As simple as these

```
PROCEDURE REASON: CYSTIC THYROID NODULE
* * * * Physician Interpretation * * * *

RESULT:
HISTORY : nodule on physical exam.

Right thyroid lobe measures 4.4 x 2.1 x 1.9 cm.  Left lobe measures 4.0 x
1.9 x 1.4 cm.  Solid mid pole nodule within it measures 0.7 x 0.6 x 0.6
cm.

The isthmus measures 0.5 cm.  Within the isthmus toward the right is a
dominant solid nodule of 2.2 x 1.2 x 1.7 cm.

IMPRESSION: Dominant solid nodule within the isthmus.  This corresponds
to the palpable abnormality.  Further evaluation is necessary.
```

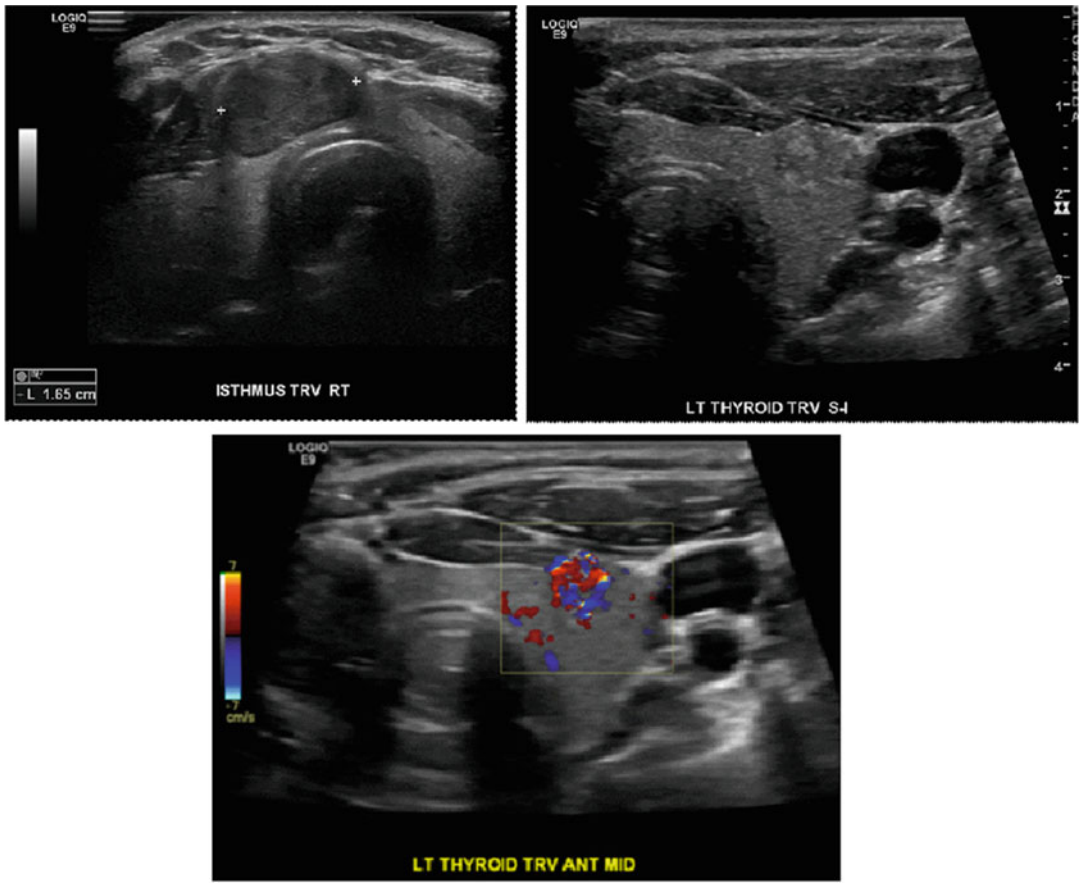


Fig. 2.2 An example of thyroid ultrasound reporting that omits key information and can impact the course of subsequent management. The ultrasound images are from the same patient in the original report, obtained on a subsequent study, and showing a hypervascular left thyroid nodule with irregular borders that was a tall cell variant of thyroid cancer

Table 2.2 The timing of thyroid ultrasound in the course of thyroid disease management

Thyroid disease	At initial evaluation	With FNA	Before surgery	At surgery	6 month follow-up	Annual follow-up[a]
Nodule/cyst	Yes	Yes	Yes	If available	Yes	Variable
Goiter	Yes	Yes	Yes	If available	Yes	Variable
Thyroiditis	Maybe[b]	Yes	Yes	If available	n/a	Maybe[b]
Graves' Disease	Maybe[b]	n/a	Yes	If available	n/a	Maybe[b]
Cancer	Yes	Yes	Yes	If available	Yes	Variable
Cervical lymphadenopathy or known metastases	Yes	Yes	Yes	If available	Yes	Yes

[a]The frequency of follow-up is somewhat controversial but can be based on risk assessment of thyroid cancer recurrence and, in benign disease, the characterization and cytology findings related to thyroid nodules or goiter
[b]Yes if considering surgical therapy or concerning findings are present on physical exam

adjustments seem (and are), they have been the source of missed central neck lymphadenopathy, parathyroid gland abnormalities, tracheal deviation, ectopic tissues, and obviously lateral neck metastatic disease. Again, the challenge lies in cultivating education and ongoing sharing of information so that more uniform practice patterns can evolve.

Where and When to Perform Thyroid Ultrasound

Ultrasound has an appropriate place in any medical setting—a radiology department, ambulatory clinic, emergency room, and operating room. For surgeons, utilization of ultrasound in the operating room can add to exposure and practical experience, facilitate teaching of residents and fellows, and may occasionally identify findings that change decision-making during surgery. Table 2.2 summarizes when in the course of thyroid disease evaluation there is a distinct role for thyroid ultrasound. If controversy can be viewed as lack of consensus, there is still controversy about some of the timing or frequency of ultrasound in long-term follow-up of both thyroid nodules and thyroid cancer [39–42]. Evidence-based parameters to inform those timing options are based on risk assessment for disease progression or recurrence [22–25, 43–45] (Table 2.2).

Standardization of Ultrasound Reporting

It should not be surprising that, if there is significant variability in the adoption of practice-based guidelines for thyroid patient care, there is also variability in the content of thyroid ultrasound reports. Physicians follow templates that have been acquired during residency or proven effective in subsequent practice. Generating a report, whether it is a clinic office note, operative note, or radiology report, is such a basic daily action in a physician's life. Documentation is a sensitive topic for many reasons, even though it is essential for patient care and communication. Reports are frequently viewed as time-consuming, administratively burdensome, and almost superfluous to discuss and, if criticized for improvement, can be a source of annoyance or offense. Yet, the issue of optimal documentation has been part of healthcare policy discussion at national levels and has gained more visible presence in professional society agendas. Consider just these key phrases in titles of the following recent publications: "gold standard for comprehensive inter-institutional

Physician Name
Department, Hospital
Logo

PATIENT:_____
MRN#_____
DATE_____

THYROID ULTRASOUND and FNA PROCEDURE REPORT

Referring Physician Name_____
REASON for ULTRASOUND : Nodule, Cancer, Goiter, Thyroiditis, Lymph node, FNA
Other_____
CONSENTS: [ ] Rationale for procedure and therapeutic options explained
[ ] Patient questions answered [ ] Written informed consent obtained [ ] Team pause made

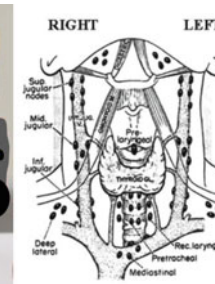
PROCEDURES PERFORMED WITH ASSOCIATED DIAGNOSTIC CODES

[ ]	DIAGNOSTIC ULTRASOUND HEAD AND NECK	CPT DIAGNOSTIC CODE
[ ]	76536 Ultrasound Soft tissues Head and Neck with image documentation	[ ] 240.9 Goiter unspec
[ ]	76942 Ultrasound guidance for needle placement	[ ] 241.0 Thyroid Nodule
[ ]	10021 Fine needle aspiration without imaging guidance	[ ] 193 Thyroid cancer
[ ]	10022 Fine needle aspiration with imaging guidance	[ ] 245.9 Thyroiditis unspec
[ ]	60100 Biopsy thyroid, percutaneous core needle	[ ] 241.1 Multinodular goiter
[ ]	76940 Ultrasound guidance for visceral tissue ablation	[ ] 246.9 Thyroid dz unspec
[ ]	76986 Ultrasound guidance intraoperative	[ ] 245.2 Hashimotos
[ ]	76999 Ultrasound procedure unlisted (ie diagnostic interventional)	[ ] Other _____

[ ] OTHER PROCEDURE

FINDINGS [ ]printed [ ]saved to PACS [ ] saved to disc ULTRASOUND NAME, PROBE, FREQUENCY

Overall thyroid appearance_____
(echogenicity, vascularity, tracheal deviation)
Right lobe: **x**y**z (cm)
Left lobe: **x**y**z (cm)
Nodules (location, size)
Features: contour, extrathyroidal extension, architecture, echogenicity, benign echogenic foci, calcifications, vascularity
Lymph nodes (cervical compartment, size)
Features: hilum, shape, calcifications, architecture, vascularity, suspicion of invasion



FNA Procedural Details (specify for each biopsy site)

Prep (Betadine or Alcohol); Anesthetic (none, lidocaine, ice cube); Onsite cytology (Y/N)
Type/gauge of needle; # of passes; Specimen prep (smear/slides, Cytolyt, flow cytometry)
Molecular markers (specimen/type); Biochemical markers (Tg, calcitonin, PTH)

Comments

MD Signature_____

Fig. 2.3 An example of a detail-oriented and illustrated thyroid ultrasound report (Adapted from Nagarakatti et al., ref 49)

Table 2.3 Information that is optimally included as part of a comprehensive, diagnostic thyroid ultrasound report

Checklist of data to include in thyroid ultrasound report	Terminology that alerts to potential for malignancy
• Patient identification • Facility identification • Examination date • Side (left or right) of anatomic site imaged • Images of normal and abnormal anatomy – Right thyroid lobe, transverse and longitudinal – Left thyroid lobe, transverse and longitudinal – Isthmus – Abnormalities • Size measurements associated with all appropriate areas, normal and abnormal, in 3 dimensions • *Global thyroid assessment related to* – Diffuse or localized abnormality – Echogenicity – Vascularity – Additional findings (pyramidal lobe, substernal extension, tracheal deviation, thyroglossal duct cyst, ectopic tissue) • *Nodule characteristics related to* – Number and location – Contour/Margins – Extrathyroidal extension – Internal composition/architecture – Echogenicity – Calcifications or other echogenic foci – Vascularity • Evaluation of lymph nodes • Evaulation of observed other pathology (parathyroid disease, other neck masses) • Cine-clips if appropriate • Plan for retention of images in medical record	Micocalcifications Irregular/interrupted thick calcifications Irregular margins Taller than wide shape Markedly hypoechoic Hypervascularity Solid Invasion beyond thyroid capsule Abnormal cervical lymph nodes

Based on reference from AIUM [28] and TCCC [48]

communication of perioperative information for thyroid cancer patients" and "statement on the essential elements of interdisciplinary communication" [46, 47].

Two up-to-date documents, one from the AIUM [28] and the other from the Thyroid Cancer Care Collaborative (TCCC, ref 48), have framed the theme of thyroid and parathyroid ultrasound reporting in very precise terms. These have been motivated by the absence of detail and the consistency of describing key details in many thyroid ultrasound reports (see Fig. 2.2). This information is critical for understanding the underlying thyroid diagnosis and for guiding eligibility for interventions, such as FNA. The AIUM and TCCC have thoughtfully prepared a comprehensive guide for what constitutes optimal content of a thyroid ultrasound report. A practical guide to initial set-up of an office-based ultrasound practice also provides a sophisticated, illustrated example of a thyroid ultrasound report (Fig. 2.3) [49]. A checklist version of these components, and the terminology that alerts to potential for malignancy, are represented in Table 2.3.

Pattern Recognition in Thyroid Ultrasound

As a concept, "risk-stratification" applies to the effort to categorize thyroid cancers according to a predicted risk of recurrence, supplementing the survival prediction of traditional cancer staging

systems [43, 44]. This innovative concept has changed the landscape of thyroid cancer management. As a terminology, "risk-stratification" subsequently also seemed to fit the concept of refining characterization of thyroid nodules to predict better the risk of malignancy. Hence, "pattern recognition of thyroid nodules for risk-stratification of cancer" was formalized into a management algorithm as part of the ATA guidelines anticipated to be published in 2015 [45]. The assessment of malignancy risk in thyroid nodules and cervical lymph nodes, based on their ultrasound appearance, is not a new concept [50–61]. It is also well known that any single ultrasound feature by itself cannot reliably discern a thyroid malignancy. However, the recognition of key patterns, collections, and combinations of features, may enhance that prediction [45]. The implication is that very low risk thyroid nodules may be able to avoid FNA until a certain higher size threshold, or possibly altogether. The implication, furthermore, is that an expectation exists for clinicians who perform ultrasound to accurately appreciate and classify these patterns. The challenge and potential controversy rest in whether consistent classification can be achieved, and whether prospectively, the cancer risks will declare themselves as predicted. Ultrasound interpretation can be subjective. Practitioners have different capabilities. Refinement of perception in order to discriminate among these new patterns may require dedication to learn new skills or reformat prior interpretations. Furthermore, the use of this new algorithm is contingent on accurate and comprehensive reporting of features. While this algorithm represents a continuation of evidence-based recommendations from the ATA in 2006 and 2009, it also suggests the beginning of a new, more meticulous phase of thyroid ultrasound interpretation. Figure 2.4 illustrates examples of this innovative ultrasound classification scheme, including that the presence of any abnormal cervical lymph nodes automatically alerts to consideration of thyroid nodules into the high-risk category.

Education and Accreditation in Thyroid Ultrasound

A number of specialty societies offer basic and advanced continuing medical education in thyroid ultrasound: Radiological Society of North America (RSNA), American College of Surgeons (ACS), American Head and Neck Society (AHNS), American Association of Endocrine Surgeons (AAES), American Thyroid Association (ATA), American Association of Clinical Endocrinologists (AACE), The Endocrine Society (TES), and the American Institute of Ultrasound in Medicine (AIUM). Most courses have both a didactic component and practical, hands-on ultrasound workshop. These courses provide knowledge but they also are the prerequisites for accreditation in thyroid (neck) ultrasonography [9, 10, 12, 62–65].

Accreditation or professional certification is achieved via completion of radiology residency or radiology subspecialty, via certification offered by ACS to surgical specialists, and via Endocrine Certification in Neck Ultrasound (ECNU, a joint effort of AACE and AIUM) to several eligible specialists (endocrinologists, cytopathologists, endocrine surgeons, otolaryngologists, and radiologists). Certification through the ACS and ECNU is a voluntary process and includes both written examination and validation of competency through proctored performance of ultrasound examination or submission of ultrasound and FNA cases [66, 67]. Successful completion of the ECNU certification entitles the candidate to use the ECNU designation with other professional degrees after their name. State credentialing boards, hospital privileging departments, and insurance payors currently do not mandate accreditation or have a uniform policy towards thyroid ultrasound credentialing. Since 2013, however, anecdotal (unpublished) reports of third party payors requiring ECNU certification for reimbursement have come to attention, and may suggest that some type of accreditation will be important for future reimbursement policies.

a

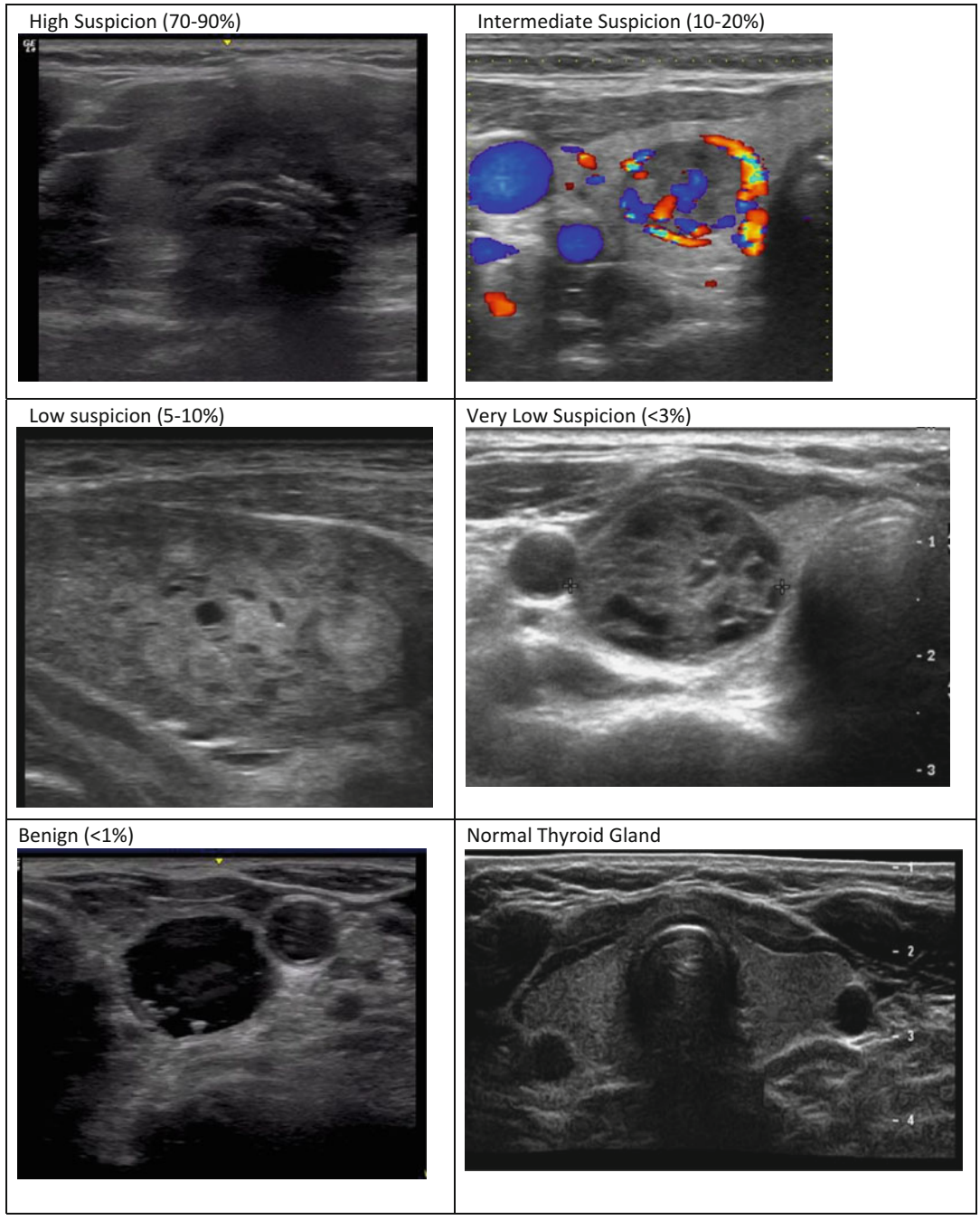
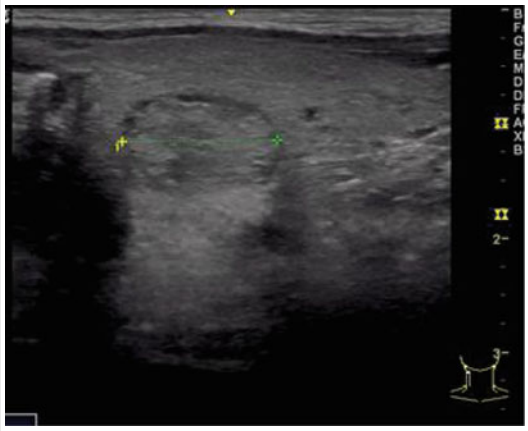


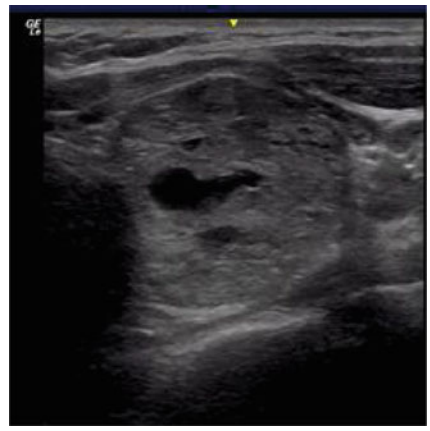
Fig. 2.4 Examples of "pattern recognition" in thyroid ultrasound. In **a**, pattern recognition refers to the classification of thyroid nodules by risk of malignancy. In **b**, examples demonstrate pattern recognition in terms of appropriate classification of individual nodule characteristics. (Based on reference 45 and commentary on anticipated 2015 ATA guidelines). In **c**, examples demonstrate lymph node metastases in the central and lateral neck

b

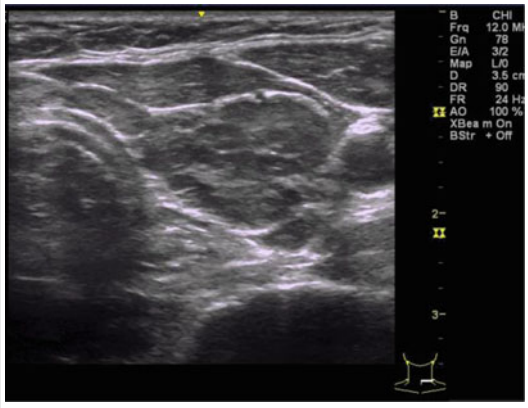
True thyroid nodule



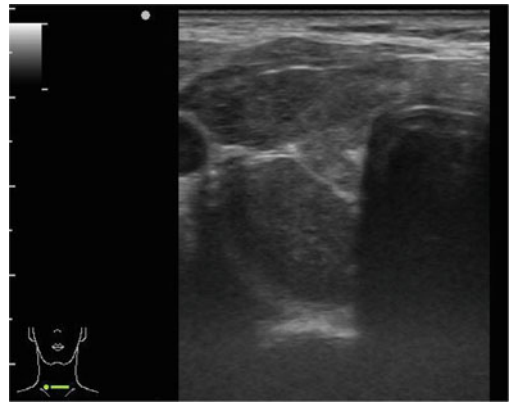
True thyroid nodule



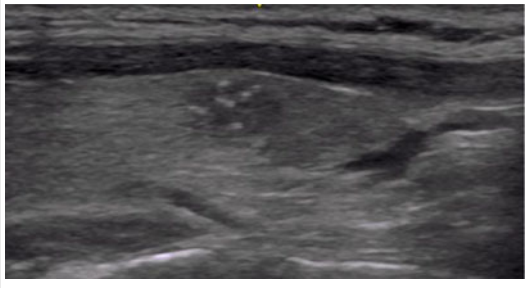
Pseudonodules (thyoiditis)



Pseudonodules (thyoiditis)



Microcalcifications in small, solid hypoechoic nodule



Colloid ring-down artifact in multi-cystic thyroid lesion (not microcalcifications)

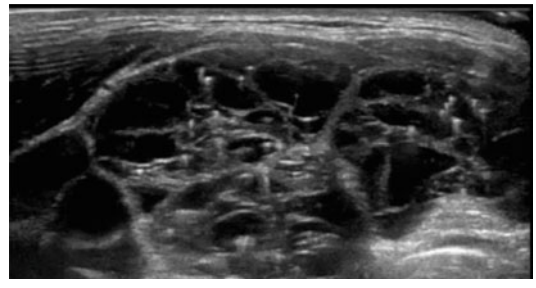
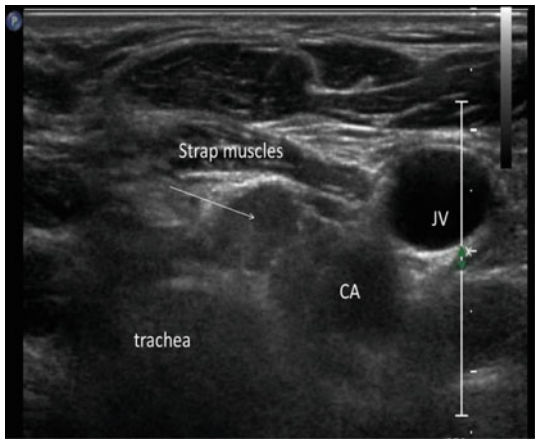


Fig. 2.4 (continued)

c

Metastatic thyroid cancer in central neck (level 6) lymph node (medial to carotid artery (CA) and jugular vein (JV)



Metastatic thyroid cancer in lateral cervical (levels 2-5) lymph nodes, lateral to CA and JV (filled with Doppler flow signals)

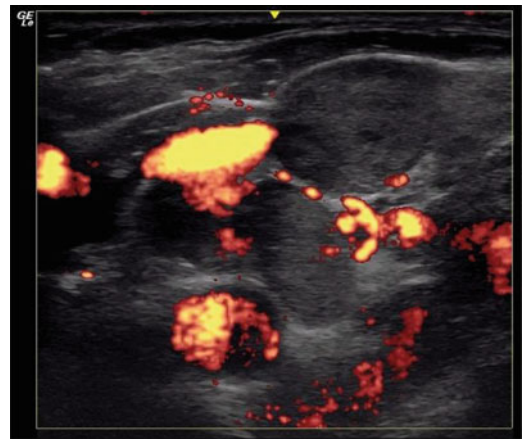


Fig. 2.4 (continued)

Familiarization with the most up-to-date educational opportunities, position statements, and society guidelines takes time. These documents are lengthy, thoughtful, concentrated with information and take time to understand. They are referenced within this chapter with the intention of conveniently having practical resources assembled and endorsed for consideration. The electronic tools and websites, likewise, provide a distinctly helpful resource as they are rich in images, not just text, imitating the essence of ultrasound.

Summary

The fundamental usefulness and versatility of thyroid ultrasound have changed the management of patients with thyroid disease and expanded usage of this technology by physicians of many specialties. Ultrasound is the primary imaging modality for thyroid disease. The controversy associated with thyroid ultrasound as it attained this status has been minimal, compared to other new technologies. The main challenges highlighted in this chapter emphasize the importance of communication, education and accreditation, and keeping pace with innovation and optimal practice guidelines. When these activities are not promoted and sustained, variability of ultrasound practice can fuel controversies which otherwise might not exist.

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Pre- and Post-Thyroidectomy Voice Assessment

3

Salem I. Noureldine and Ralph P. Tufano

Introduction

Thyroidectomy is considered the mainstay of treatment for nearly all thyroid cancers, including certain benign pathologies when indicated or elected by patients [1]. In the modern era, these procedures are being undertaken by a variety of surgeons with different training backgrounds and philosophies, that range from general surgeons and otolaryngologists to highly specialized endocrine surgeons and head and neck endocrine surgeons in high-volume academic centers. Yet, in the United States, the vast majority of thyroid surgeries are performed by low-volume surgeons who perform less than 5–10 thyroid cases a year [2]. This fact is at odds with the known relationship between volume and outcome for thyroid surgery.

Thyroidectomy is reportedly associated with a 25–84 % risk of postoperative voice alteration [3–7]. Iatrogenic recurrent laryngeal nerve (RLN) injury may in part be responsible for some of this alteration. Mechanisms of iatrogenic RLN injury may include mechanical (i.e., compression, crush, stretch, and laceration), thermal, or vascular (i.e., ischemic injury) factors [8]. Nonetheless, the presence or absence of RLN dysfunction does not solely predict functional voice outcome after thyroidectomy. Other mechanisms can affect vocal fold function, including injury to the external branch of the superior laryngeal nerve (EBSLN), postoperative inflammation, laryngeal edema, surgical trauma to the cricothyroid muscle or cricoarytenoid joint, endotracheal intubation-related trauma, and laryngotracheal fixation [9–11]. Vocal manifestations from these various pathologies can range from a seemingly normal voice or transient voice fatigue to profound and permanent dysphonia with a substantially adverse impact on the patient's quality of life [7].

Assessment of vocal fold function is important in both the pre- and postoperative evaluation of patients undergoing thyroid surgery. This will detect an existing preoperative RLN palsy or an early iatrogenic RLN injury [12]. Although most postoperative voice changes resolve spontaneously within 3–6 months of thyroid surgery, patients can develop maladaptive compensatory mechanisms during postoperative recovery [13–15]. Such vocal behaviors can persist after resolution of the underlying vocal pathology and

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are most appropriately evaluated and treated by experienced speech-language pathologists. Early identification of voice dysfunction and referral to a speech-language pathologist for vocal rehabilitation could be beneficial to these patients so that vocal function can be optimized. Therefore, postoperative voice assessment should be initiated early and include comprehensive voice-specific functional and physical evaluations.

Prevalence of Recurrent Laryngeal Nerve Paralysis

When reading the pertinent literature, it becomes obvious that the true incidence of temporary and permanent vocal fold paralysis (VFP) after thyroid surgery is still unknown. The majority of previous studies that have examined the incidence of VFP have lacked adequate postoperative vocal fold motion assessment. In fact, most studies have not incorporated direct visualization of the vocal folds as part of their postoperative assessment [5, 16, 17]. Also, there is considerable variation in the reported incidence of VFP due to the different methodology used to diagnose RLN injury, with each method having significantly different sensitivities and specificities. This is clearly demonstrated in the meta-analysis performed by Jeannon et al. [7], as a wide variation in the reported VFP rates following thyroid surgery can be appreciated. The incidence of temporary VFP ranges from 1.4 to 38. 4 % with an average value of 9.8 %, while the incidence of permanent VFP varies 10-fold, according to the method of laryngeal exam and ranges from 0 to 18.6 % with an average value of 2.3 % (Fig. 3.1).

Such statistics about the true risk of RLN injury with subsequent temporary or permanent VFP rates are important in obtaining informed patient consent before proceeding with thyroidectomy. Nondisclosure can cause potential unfavorable effects on the patient–physician relationship and health outcomes [18]. Moreover, the low rates of VFP quoted to patients preoperatively by surgeons are often derived from reported series of patients treated at high-volume academic centers with favorable and publishable results. This information for counseling should be based on knowing one's personal outcomes and can only be accurately obtained through reasonable volume. Ultimately, uniform and standardized criteria for vocal fold evaluation before and after surgery are needed in order to allow comparison of results among different centers.

Laryngeal Examination of the Larynx Versus Subjective Voice Assessment

The reason for including laryngeal exam of the larynx in all patients undergoing thyroidectomy, both pre- and postoperatively, is basically due to the fact that VFP may occur without any voice alterations [5]. This discrepancy between glottic function and voice may be due to the variability in the remaining function of the vocal fold, position of the paralyzed cord, or compensation of the contralateral vocal fold [19].

It is common to notice improvement in voice symptoms in a patient with a stable VFP. This may be due to the resumption of normal vocal fold function or, just as likely, the evolution of a more favorable medial position with ongoing stable VFP [20, 21]. Without laryngeal exam, such improvement could be falsely interpreted as a resolution of the VFP. The correlate is also true that change in voice may derive from many sources and does not necessarily imply VFP. It is only the laryngeal exam that can accurately identify VFP.

Voice Alteration with Normal Vocal Fold Mobility

After thyroidectomy, both subjective and objective voice changes may occur in patients while maintaining intact vocal fold mobility. Subjective changes may consist of voice fatigue and difficulty with high pitch. Objective findings

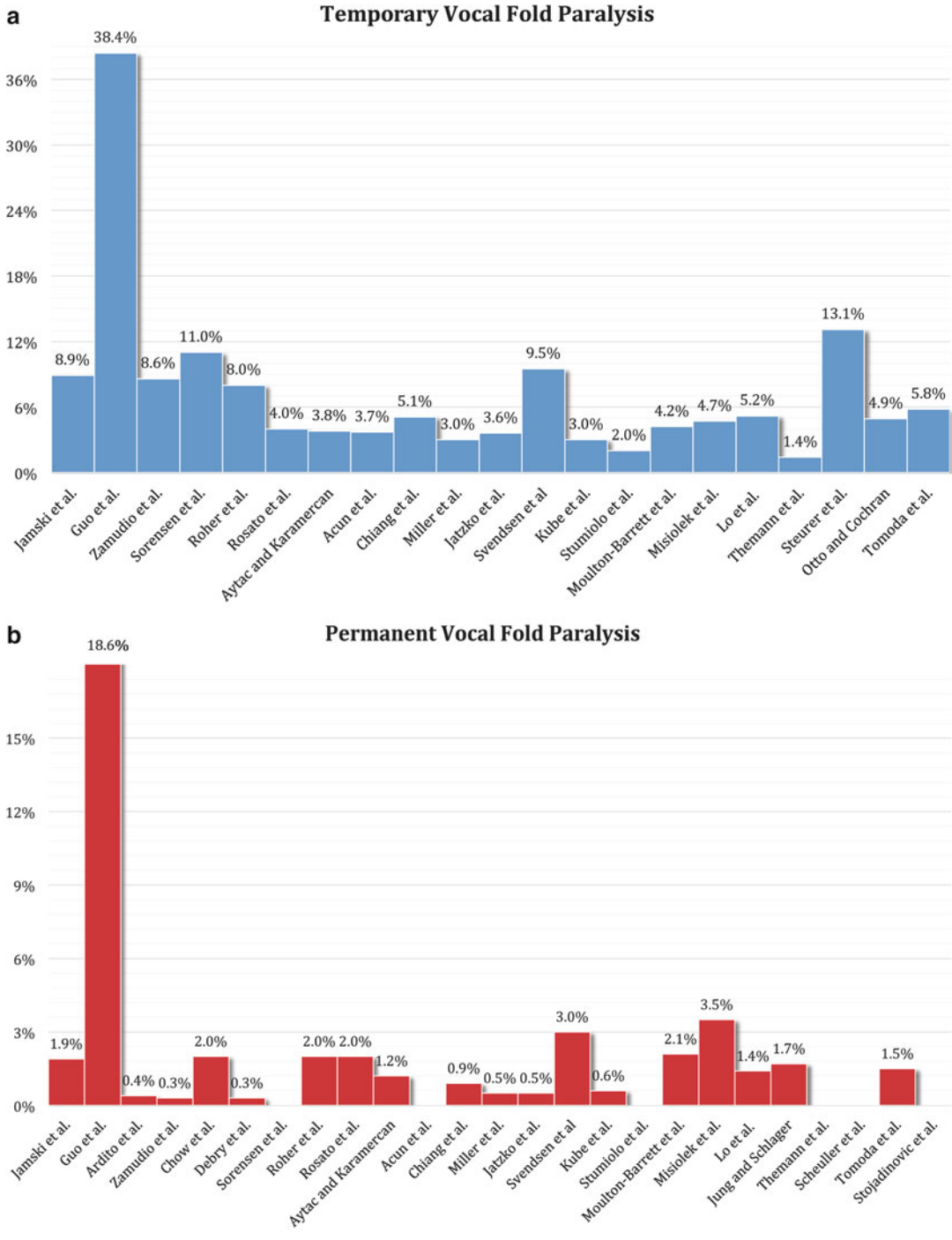

Fig. 3.1 Meta-analysis performed by Jeannon et al. [7] on 25,000 patients. (**a**) The overall incidence of temporary VFP and (**b**) permanent VFP amongst studies included in the analysis

include decrease in the voice fundamental frequency, vocal range, maximum sound pressure, vocal jitter, and phonation time [13–15]. Subjective and objective voice changes usually occur transiently in up to 80–85 % of patients after thyroidectomy with normal vocal fold function [5, 22].

The mechanisms for voice alteration despite normal vocal fold mobility include the following [9–11, 23, 24]:

- Cricothyroid muscle dysfunction: this may occur due to direct injury during thyroidectomy, transient myositis, or the effect of seroma formation.
- Injury to the EBSLN during thyroidectomy.
- Postoperative soft tissue changes affecting the larynx, including edema, strap muscle retraction, and denervation, and laryngotracheal scarring.
- Strap muscle division during thyroidectomy.
- Intubation-related vocal fold changes: these include short-term edema, vocal fold laceration, arytenoid dislocation, or more long-term vocal fold granuloma formation.
- Upper respiratory tract infection: typically a viral laryngitis unrelated to surgery.

What is important to note is that patients do not usually communicate subtle voice changes, and this may pose difficulty for unmindful surgeons to pick up. To overcome this issue, various Voice Handicap Index (VHI) questionnaires have been used and are reliable in identifying voice dysfunction after thyroidectomy. Typically, patients with a change in VHI score greater than 25 from their preoperative baseline are referred to speech-language pathology and laryngology for further assessment [25]. Despite these techniques, we believe all patients need a laryngeal exam if we are to appreciate an accurate quality outcome measure of thyroidectomy.

Asymptomatic Vocal Fold Paralysis

An asymptomatic normal voice is reported to occur in 20 % of patients with VFP, falsely suggesting resolution or absence of RLN injury [26]. Various mechanisms have been suggested to explain this occurrence and include [20, 21, 26]:

- RLN sustaining partial neural function (i.e., paresis).
- A more medial position of the paralyzed vocal fold.
- Compensation of the contralateral vocal fold.

This issue highlights the significance of preoperative laryngeal assessment in patients being evaluated for additional surgery that risks injury to the RLN. Respiratory morbidity and swallowing safety may be further compromised if the contralateral nerve is operated on.

Preoperative Laryngeal Exam

Because of the relatively low overall rate of preoperative VFP in patients undergoing thyroid surgery, some have abandoned preoperative laryngeal assessment, while others have reserved it for specific cases (i.e., previous neck surgery, voice symptoms). We believe that it is very wise to routinely examine vocal fold function in all patients undergoing thyroid surgery. The rationale for this routine assessment is summarized below [12, 20, 27, 28]:

- Preoperative VFP is commonly encountered and has been reported to occur in 1.9–3.5 % of cases with benign thyroid pathology.
- VFP can be present in the absence of voice changes. The sensitivity of voice change in predicting VFP is only 30–70 % [12, 20].
- It provides a baseline for postoperative laryngeal assessment.
- VFP can suggest invasive malignancy (i.e., Stage 4 disease) preoperatively. This will prompt for more appropriate airway and lymph node imaging preoperatively and more specific patient counseling.
- Preoperative knowledge of vocal fold functioning helps to plan the management of an invaded RLN found at surgery.
- It is important to assess preoperative vocal fold function before assuming responsibility for any VFP found postoperatively.

- For accurate quality assessment, postoperative vocal fold function assessment implicitly requires preoperative examination as well.

Unfortunately, guidelines from professional bodies in the United States are lacking on this topic, and no consensus is available. The current American Thyroid Association (ATA) guidelines and the American Association of Clinical Endocrinology (AACE) guidelines make no reference on this issue. Only the guidelines from the American Academy of Otolaryngology—Head and Neck Surgery recommend laryngeal examination for patients with preoperative voice changes, for those undergoing reoperative surgery, or for patients scheduled to undergo thyroidectomy for cancer [29]. On the other hand, the British Thyroid Association (BTA) recommends laryngeal examination for patients with preoperative voice changes and for those scheduled to undergo thyroidectomy for cancer. The British Association of Endocrine and Thyroid Surgeons (BAETS) recommends that all patients should undergo pre- and postoperative laryngeal examination. Similarly, the guidelines of the German Association of Endocrine Surgeons recommend pre- and postoperative laryngoscopy in all patients undergoing thyroid surgery.

Postoperative Laryngeal Exam

Routine postoperative laryngeal exam is required in all patients undergoing thyroid surgery. This will allow surgeons to detect early iatrogenic injuries and obtain accurate information regarding their surgical outcomes. The earlier the vocal folds are assessed, the higher the incidence of abnormalities observed. Dionigi et al. [16] determined that the VFP rate was 6.4 % on the day of surgery, 6.7 % on day 1, 4.8 % on day 2, 2.5 % on day 14, and 0.8 % at 6 weeks postoperatively. This study demonstrates that the ideal time period during which to evaluate vocal fold function is the early postoperative period, as such timing will allow for the most cases of VFP to be identified.

The rationale for the routine postoperative assessment of vocal fold function is summarized below [20]:

- It is the only accurate postoperative outcome functional measure of RLN integrity. Voice abnormalities may occur in the absence of VFP; hence, for the functional and psychological recovery of the patient's symptoms in these cases, it will confirm that no injury took place to the RLN.
- Allows interpretation of surgical technique and, if utilized, intraoperative electromyography responses.
- Implications for respiratory and swallowing safety after thyroidectomy. Occasionally, a patient will not have airway symptoms in the immediate postoperative period (because the airway may be sufficient despite a paralyzed vocal fold) and the patient may present at a follow-up visit complaining of shortness of breath or stridor on exertion.

The current ATA management guidelines make no reference on this issue. The BTA guidelines recommend postoperative laryngeal exam only when there has been a voice disturbance beyond 2 weeks. Only the BAETS and the American Academy of Otolaryngology—Head and Neck Surgery have recommended that laryngoscopy should be performed postoperatively for all patients undergoing thyroid surgery.

Feasibility of Laryngeal Examination

Due to the difference in background and training of thyroid surgeons, some might feel it to be necessary to refer patients to specialized otolaryngology clinics for vocal fold assessment. We advise that all surgeons performing thyroidectomy to become confident with the technique of laryngoscopy and consider examining their patients routinely. Vocal fold function can be assessed by various modalities. The most commonly used methods include indirect laryngoscopy (mirror

examination), videostroboscopy, and fiberoptic laryngoscopy (FOL). Significant differences in reported rates of VFP have been documented when comparing these modalities [7].

Although indirect laryngoscopy is simply performed, it has a restricted visual field and low diagnostic accuracy [30]. A significant percentage of patients cannot tolerate this method of examination due to the gag reflex. Conversely, videostroboscopy utilizes a high frequency strobe light to analyze the vibration and the mucosal wave of the vocal folds during phonation. It requires specialist equipment and therefore restricted to specialist practice and is not a feasible method of assessing voice function after thyroidectomy in routine practice. FOL offers a more detailed and wider field of vision to the larynx compared with indirect laryngoscopy (Fig. 3.2). The optical illumination and magnification can also allow the images to be portrayed on a screen for higher definition assessment. FOL should be considered the gold standard in diagnosing perioperative VFP since it is easily tolerated by patients and can be performed quickly in the office. Usually the scope is advanced above the epiglottis and with the "e" and "sniff-in" maneuver; adduction and abduction of the true vocal folds can be appreciated. On average, only 6 exams are needed for a beginner to become competent in performing FOL [31].

FOL should be performed within the first 24 h after surgery. We and others believe that early laryngeal assessment, within the first 24 h after surgery, is the optimal time frame during which to detect the majority of VFP cases, including mild impairments that begin to undergo the healing process within the first few days following surgery but still require follow-up [16].

The relative cost of the selected laryngeal examination modality should be considered. While there is no incurred cost of indirect laryngoscopy using a laryngeal mirror, there are additional health care costs in performing FOL and videostroboscopy. These modalities are justified in select cases when the larynx cannot be adequately examined using the laryngeal mirror or in the case of identified vocal fold motion impairment in order to more accurately define the abnormality [29]. Nevertheless, the surgeon assessing laryngeal function should strive to perform the most complete, cost-effective examination for the patient and document the examination accurately.

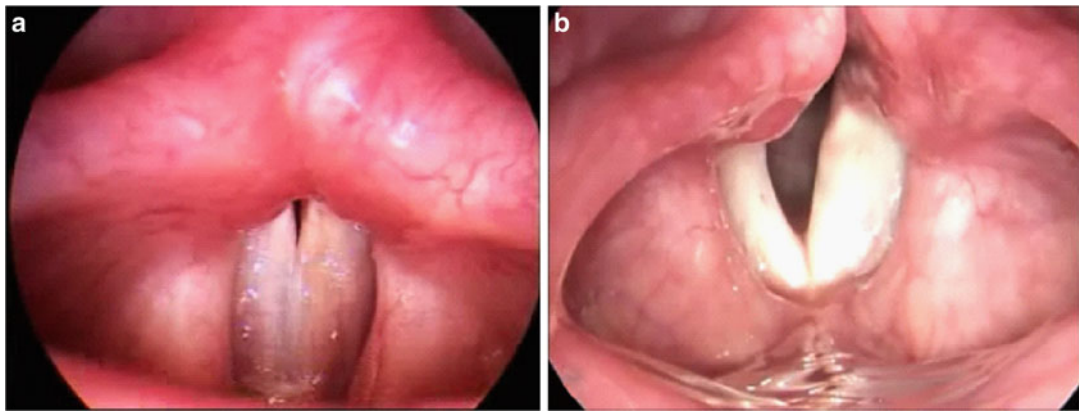

Fig. 3.2 Fiberoptic laryngoscopy assessment after total thyroidectomy. (**a**) Both right and left vocal folds are mobile during phonation. (**b**) Right vocal fold paralysis during phonation. (Courtesy of Alexander Hillel, MD. Used with permission.)

Feasibility of Transcutaneous Laryngeal Ultrasonography

Recently, transcutaneous laryngeal ultrasonography (TLUSG) has been proposed as a promising, noninvasive technique to examine the vocal folds during thyroid surgery [32–36]. Because most patients with thyroid disease are submitted to ultrasound examination during their clinical evaluation, this method of evaluating vocal fold mobility could become a real asset in the preoperative and postoperative management of patients undergoing thyroid surgery. Some advantages of TLUSG over direct laryngoscopy are its noninvasiveness, convenience, comfort, increased availability, and obviation of topical anesthetics. In addition, the use of in-office ultrasound has been shown to be cost-effective in clinical practice.

The greatest enthusiasm for this technique was historically in the pediatric population, in whom laryngoscopy is not well tolerated without anesthesia [37]. However, recent studies have had favorable findings in the adult population, demonstrating the reproducibility of TLUSG in identifying postoperative VFP with accuracy similar to direct laryngoscopy. Studies have estimated that nearly two thirds of laryngoscopies could be avoided by the use of preoperative screening TLUSG [33]. Despite these favorable findings, the vocal folds cannot be assessed by TLUSG in approximately 20–25 % of patients, thus requiring direct laryngoscopy [33–35, 38]. Moreover, the sensitivity of TLUSG in demonstrating VFP ranges from 60 to 95 % [32–34, 39, 40]. Factors such as male gender, advanced age, increased body habitus, calcification of the thyroid cartilage, sharp angulation of the thyroid cartilage, and distance from collar incision to thyroid cartilage, as well as the experience of the ultrasonographer, have all been cited to affect the accuracy of TLUSG [38, 41]. Even for some patients whose vocal folds are assessable by TLUSG, their findings can be discordant when compared with the gold standard, direct laryngoscopy. Therefore, the routine use of TLUSG as a diagnostic or screening test remains controversial.

Summary

Although the true rate of RLN injury after thyroid surgery is still unknown, we know for a fact that it is common, occurring in as many as 10 % of patients on average. Even in the absence of RLN injury, voice changes frequently occur after thyroid surgery. Only routine pre- and postoperative laryngeal assessment will allow surgeons to consistently make informed clinical decisions that will improve outcomes and assess objectively the impact of the operation of vocal fold function. We believe this to be the only reliable way that allows immediate accurate assessment of the surgical technique used. This will optimize surgical training and provide valid, accurate surgical outcome data to patients.

Conflicts of Interest Disclosures All authors report no conflicts of interest.

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Intraoperative Neuro-monitoring of the Laryngeal Nerves During Thyroidectomy

4

Yinin Hu, John B. Hanks, and Philip W. Smith

Introduction

Intraoperative neuro-monitoring (IONM) allows the evaluation of laryngeal motor integrity during and following operative dissection. Its primary roles are in the delineation of nerve anatomy and the early detection of operative injury. Within this chapter, normal and anomalous pathways of the recurrent laryngeal nerve are described. Electrophysiologic principles of intraoperative neuro-monitoring will be summarized, with a focus on models that use electromyographic outputs, most commonly via electrode-laden endotracheal tubes. Finally, the evidence behind the use of IONM in thyroid operations will be reviewed.

Anatomy

Vagal Innervation of the Larynx

The entire laryngeal apparatus is innervated by the vagus nerve and its branches. The vagus arises from the medulla in the brainstem and passes through the jugular foramen of the skull. It is associated with two sensory ganglia: the superior (jugular) ganglion and the inferior (nodosum) ganglion. The nodosum ganglion is just caudal to the jugular foramen. As the vagus nerve passes into the neck, it enters the carotid sheath, lying posterior to, and between, the internal jugular vein and the internal carotid artery.

Superior Laryngeal Nerve

The superior laryngeal nerve (SLN) takes off from the main trunk of the vagus immediately after its exit from the jugular foramen. The SLN descends to the pharynx traveling medial to the carotid sheath. It then divides into the internal and external branches approximately 2–3 cm above the superior pole of the thyroid. The internal branch of the SLN conveys general sensation including pain, temperature, and touch for the entire laryngeal apparatus superior to the vocal folds.

External Branch of the Superior Laryngeal Nerve

The external branch of the SLN (EBSLN) provides motor function to the inferior constrictor muscles and the cricothyroid muscles of the larynx. This branch enters the cricothyroid muscle

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laterally and contributes innervation to the pharyngeal plexus. The anatomic course of the EBSLN is highly variable, and was categorized based on risk of injury by Cernea and colleagues [1, 2]. A nerve crossing the superior thyroid artery greater than 1 cm above the upper border of the superior thyroid pole was classified as Type 1, while a nerve crossing within 1 cm of this plane was classified as Type 2 (Fig. 4.1). Anatomy was further subdivided into Types 2a and 2b based on whether the nerve crossed above or below the superior border of the superior thyroid pole. Type 1 is most common (40–60 %), while Types 2a and 2b combine to comprise 30–40 % of cases [3]. Type 2 nerves are at increased risk of iatrogenic injury due to its proximity to the superior thyroid vessels in the field of dissection for thyroidectomy. Additional variants have since been described, including instances in which the EBSLN crosses distal to the ramification of the superior thyroid artery [4]. Importantly, roughly half of patients have asymmetrical EBSLN anatomy.

Recurrent Laryngeal Nerve

The recurrent laryngeal nerve (RLN) and its anatomy are important to all thyroid surgeons. The right and left RLNs are asymmetrical in their course in the neck due to the embryologic development of the third and fourth branchial arches. The right RLN branches from the right vagus nerve anterior to the right subclavian artery. It then passes inferior and posterior to the right subclavian artery and ascends in the neck between the trachea and esophagus (Fig. 4.2). The left RLN arises from the left vagus nerve within the thorax and travels inferior and posterior to the arch of the aorta at the level of the ligamentum arteriosum. It then ascends within the neck between the trachea and the esophagus. The left RLN lies more predictably directly within the tracheoesophageal groove in the surgical field of thyroid surgery, while the right RLN takes a more oblique course and is more variable in its position in the lower portions of the surgical field. The right RLN typically may be found within 1 cm of the tracheoesophageal groove at the level of the lower border of the thyroid, and travels within the groove as it courses cephalad. Both RLNs travel superiorly, deep to the inferior border of the inferior pharyngeal constrictor muscle just posterior to the cricothyroid joint. They supply the interarytenoid, posterior cricoarytenoid, and the lateral cricoarytenoid muscles. The RLN on both sides contain motor fibers which innervate the intrinsic muscles of the larynx as well as both sensory and motor fibers to the glottis, sub-glottis, and trachea. Of intrinsic laryngeal muscles, only the cricothyroid muscle, which is innervated by the external branch of the superior laryngeal nerve, is not innervated by the RLN [5].

It is important to realize that the RLN often branches before entering the larynx. Usually, this branching will occur superior to the inferior thyroid artery, but also may occur more caudally in its course. The extra-laryngeal branches have been described as functionally separate fibers. The anterior branches are thought to provide motor supply to the larynx, including the adductor muscles [6]. Although the consistency of the functional separation between motor and sensory fibers within the anterior and posterior branches is unclear, it is important to realize that extralaryngeal branching does occur, and that injury of an anterior branch may have significant motor impact even if it is the smaller caliber branch. Between 23 % and 34 % of RLNs bifurcate prior to entry into the larynx. Among roughly one-fourth of these patients, bilateral bifurcations are present and frequently demonstrate symmetric branching patterns [6–8].

Right Nonrecurrent Laryngeal Nerve

An important variation in the course of the RLN on the right is the existence of a nonrecurrent path to the larynx. The incidence of a nonrecurrent right laryngeal nerve is in the range of 0.4–2.4 % on the right and less than 0.05 % on the left [9]. Due to embryologic maldevelopment, this nerve variant is associated with an anomalous right subclavian artery, termed arteria lusoria. In this variant, the right carotid and subclavian

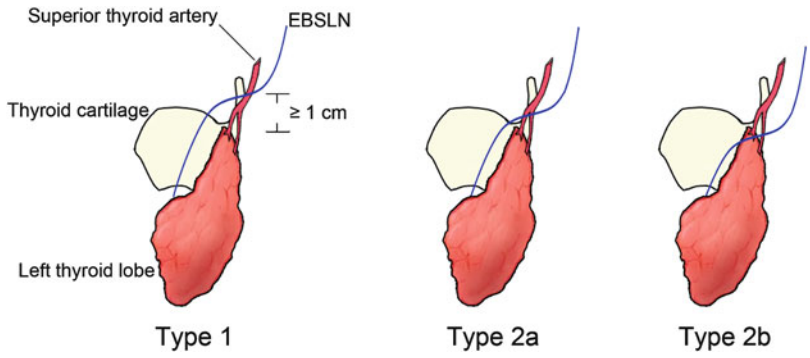

Fig. 4.1 Cernea classification for anatomic variants of the external branch of the superior laryngeal nerve (EBSLN). Type 1: nerve crosses the superior thyroid vessels 1 cm or more above the superior thyroid pole. Type 2: nerve crosses the superior thyroid vessel less than 1 cm from the superior thyroid pole, either *above* (Type 2a) or *below* (Type 2b) the superior border of the thyroid

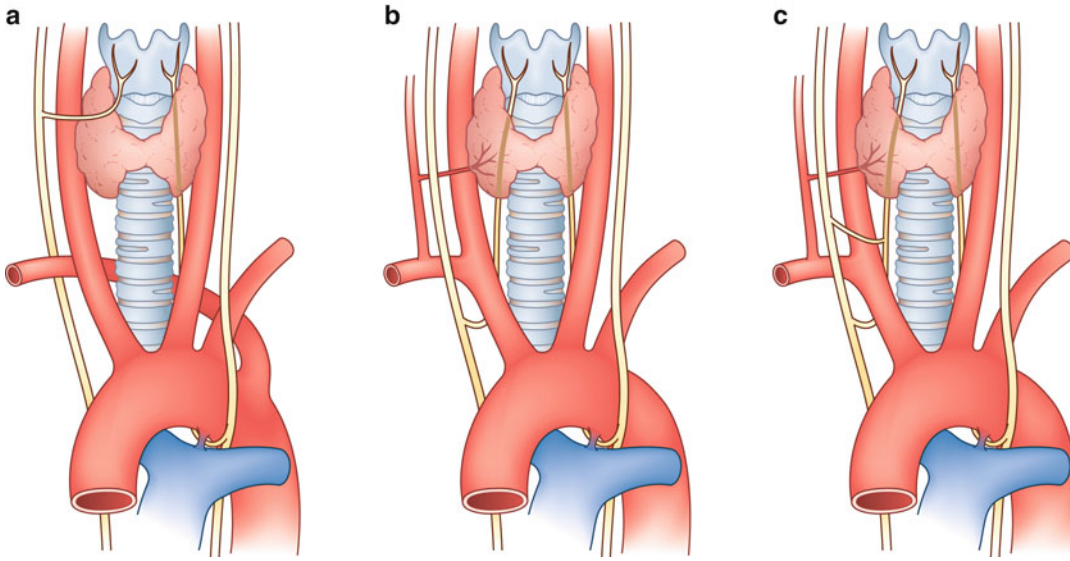

Fig. 4.2 Anomalous variations of the right recurrent laryngeal nerve. (**a**) A nonrecurrent right laryngeal nerve in the setting of an aberrant right subclavian artery origin. (**b**) Normal anatomy of the recurrent laryngeal nerves. (**c**) The rare anomaly of both a recurrent and a nonrecurrent right laryngeal nerve joining distally in the setting of a normal right subclavian artery anatomy. [*Source*: Sabiston Textbook of Surgery: The Biological Basis of Modern Surgical Practice, 19th Edition, Townsend CM, Beauchamp RD, Evers BM, Mattox KL, p. 887, Copyright Elsevier (2012)]

arteries do not arise as bifurcations of a common trunk. Rather, the aberrant right subclavian artery arises directly from the arch of the aorta distal to the origin of the left subclavian and passes posterior to the esophagus. This finding may be associated with dysphagia, but frequently is asymptomatic. In these situations, the right inferior laryngeal nerve takes off directly from the vagus and passes either inferiorly or laterally along the course of the inferior thyroid artery directly to its entrance in the larynx near the ligament of Berry [10] (Fig. 4.2). Interestingly, the widespread use of preoperative ultrasound examination has led to the increased detection of the aberrant takeoff of the subclavian artery. The anomaly also is well visualized in those patients who have had CT or MRI obtained prior to surgery. Therefore, through noninvasive preoperative

evaluation, the surgeon can be warned about the existence of this important aberrant anatomy [9, 11].

Since the early 1900s, pioneers of thyroid surgery Dr. Kocher and Dr. Billroth were aware of the damage inflicted upon patients through unilateral or bilateral RLN injuries while operating on large thyroid goiters. They advocated minimizing risk of nerve injury by avoiding exposure of the nerve. Several decades later, Dr. Lahey and others advocated routine exposure of the nerve and tracing its course in the tracheoesophageal groove in order to minimize damage. For several decades, it was not firmly established which was the preferable technique to minimize nerve injury. More recent literature has demonstrated that routine identification of the RLNs is associated with decreased rates of transient and permanent nerve injury and this is widely considered the gold standard [12].

As thyroid and parathyroid surgery became more widespread, two issues have presented themselves concerning minimizing the risk of nerve injury: First, demonstrating an anatomically intact nerve during the case did not necessarily correlate with functional performance postoperatively. Second, the inability to directly measure vocal cord performance intraoperatively left uncertainty with regard to the ultimate postoperative outcome. As a result of these issues, the technique of intraoperative monitoring of the RLN and external branch of the superior laryngeal nerve have been investigated and reported extensively in the literature.

Introduction to Neuro-monitoring

In the most basic sense, intraoperative neuromonitoring of the RLN may be defined as any technique that stimulates the nerve and assesses evidence of an intact neural impulse downstream. In the operative setting, nerve stimulation is accomplished by direct transmission of an electrical impulse from a stimulator probe. This impulse produces a current along the nerve in the form of action potentials, transmitted through ion flow. In the presence of an intact RLN, this current is manifested distally via muscle contractions. These contractions are then registered through direct visual observation, pressure response monitoring, or using biopotential electrodes which sense ion distributions on the tissue surface (electromyography, EMG). In the case of EMG, the input to the sensing biopotential electrode is juxtaposed against a reference (or grounding) electrode placed on an electrically neutral tissue (Fig. 4.3).

EMG response is more nuanced than simply being present or absent. The amplitude and latency of EMG signals produced by nerve stimulation are also of value in the interpretation of IONM results. Latency (in milliseconds, ms) is the time required for an electrical impulse to travel from the stimulation site to the recording site and is directly related to the anatomic length of the electrical pathway. Amplitude (in microvolts, μV) is measured by the height in between the positive EMG waveform's apex and the negative waveform's trough and reflects the summative electrical activity of individual muscle fibers. The vagus, recurrent laryngeal, and external branch of the superior laryngeal nerves each have characteristic latency and amplitude values that can be interpreted in order to optimize the negative predictive capacity of IONM (Fig. 4.4). Recent work by Sritharan and colleagues documented normative values for these three nerves from 25 consecutive patients [13]. Using an endotracheal tube with surface electrodes to detect target muscle response, the authors report mean latency measurements of 8.14 ms and 5.47 ms for the left and right vagus nerves, respectively. Latency values for the recurrent laryngeal and external branch of the superior laryngeal nerves were less variable bilaterally, with pooled values of 3.96 ms and 3.56 ms, respectively. Mean amplitude was 739.7 μV for the vagus nerve, 891.6 μV for the RLN, and 246.6 μV for the external branch of the superior laryngeal nerve. In a related study of 1000 nerves at risk (three with permanent vocal cord paralysis), Genther and colleagues posited a minimum post-dissection amplitude of 200 μV to accurately predict normal neural function with a positive predictive value of

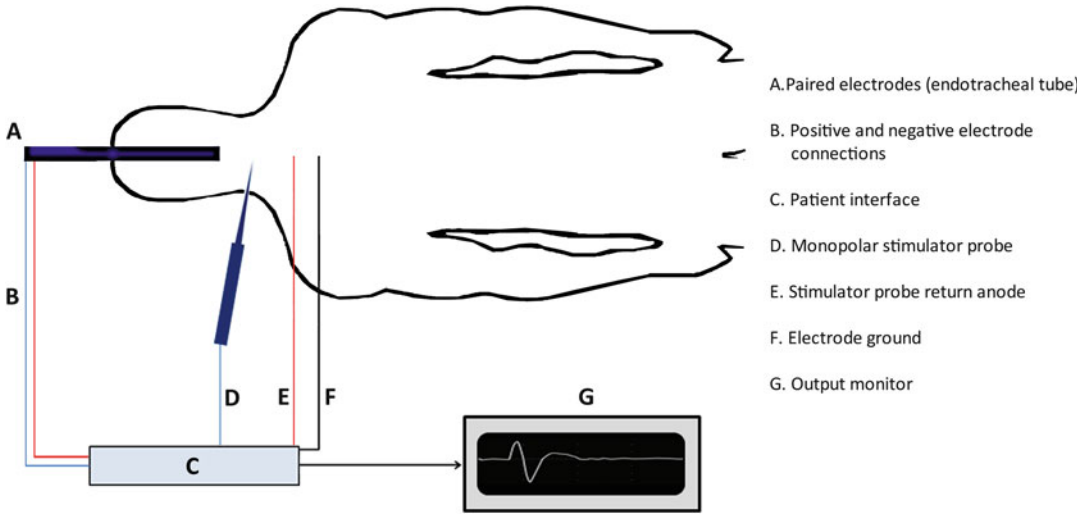

Fig. 4.3 Intraoperative neuro-monitoring instrument setup with monopolar stimulator probe and electrode-laden endotracheal tube for electromyography output

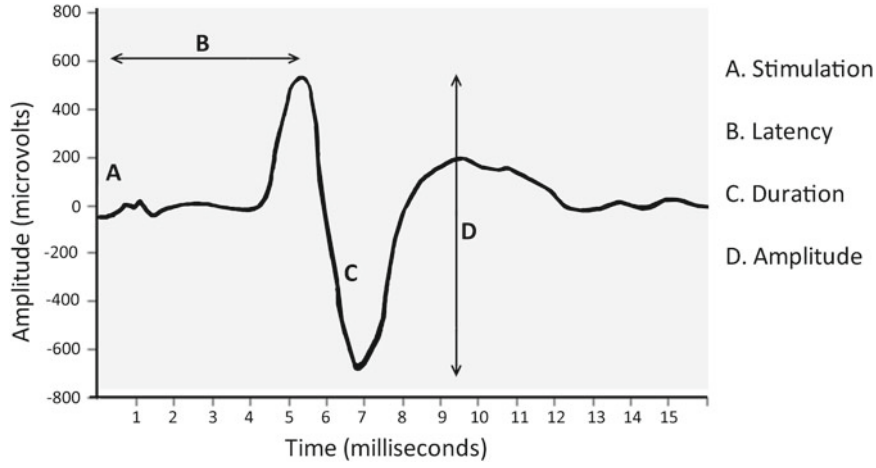

Fig. 4.4 Electromyographic waveform. Simulation probe signal (A) is detected first, followed by the latency period (B). The latency period, along with the duration (C) and the amplitude (D) of the electromyographic signal, is relevant to the likelihood of transient or permanent injury

72 % and a negative predictive value of 99.9 % [14]. Using these values as a reference framework and comparing pre- and postoperative IONM measurements, a discerning surgeon can accurately verify the presence of an intact and well-transmitting neural pathway.

Over the last 10 years, several methods of IONM have been described, differing primarily in the techniques used for the assessment of the distal impulse:

Direct Observation

1. Endoscopic observation of posterior cricoarytenoid contraction.
2. Laryngoscopic observation of posterior cricoarytenoid contraction.

Pressure Monitoring

1. Palpation of the cricothyroid or cricoarytenoid muscle.
2. Glottic pressure response monitoring of the endotracheal tube pressure during RLN stimulation.

Electromyography

1. Endoscopic placement of intramuscular vocal cord electrodes.
2. Direct placement of intramuscular vocal cord electrodes through the cricothyroid membrane.
3. Specialized electrodes placed on and in the endotracheal tube, directly contacting the vocal cord mucosa.
4. Post-cricoid surface electrodes placed in the post-cricoid space.

Continuous Neuro-monitoring

Regardless of the signal detection modality, classic IONM methods require the operator to intermittently stimulate the vagal nerve or RLN within the dissection field to verify integrity intraoperatively. Therefore, this method inherently leaves the patient susceptible to nerve injury in between stimulations. As a result, the ability for classic IONM to *prevent* nerve injury—rather than simply identifying injuries that have occurred—has been questioned. More recently, continuous neuro-monitoring has emerged as an amendment to EMG IONM, whereby an electrode fixed directly upon a segment of the vagus nerve provides automated, periodic, low-level stimulation every few seconds. If thresholds for amplitude or latency are violated during dissection, the operating surgeon is alerted to impending injury.

Limitations

Using any or all of these methodologies, the technology of IONM has numerous limitations. These can be classified into several categories.

1. Setup failure. A number of pitfalls in equipment setup can result in a false-positive indication of injury. A dislodged grounding wire can result in an inactive detection device. Intraoperative rotation of the endotracheal tube can cause sensing electrodes to lose contact with the target tissue. Finally, setting the nerve stimulator level too low or the detection event threshold too high can have the same falsely positive result.
2. Nerve stunning. A traumatized or "stunned" RLN may give a negative stimulation value intraoperatively, but may in fact remain intact and be functional by the completion of the procedure.
3. Medications. During induction, inadvertent muscle relaxant administration may impair target muscle response in the setting of an intact neural impulse.
4. Falsely normal readings may arise if the endotracheal tube carrying the electrode is placed too far distally into the trachea. This placement detects direct stimulation of the trachea or paratracheal tissue, which could transmit the current and produce a positive EMG response.
5. Stimulator misplacement. A transected nerve could produce a falsely normal result if the monitor is erroneously replaced on the distal nerve segment closer to the target muscles than the injured nerve segment.

Technique Overview

Effective IONM begins in the preoperative setting with anesthesia considerations. A short-acting neuromuscular blocking agent should be chosen for induction, after which neuromuscular blockade should be avoided. The endotracheal tube position should be verified under direct or video laryngoscopy such that the exposed electrodes are in direct contact with the true vocal cords. Subsequent rotation of the endotracheal tube intraoperatively should be avoided, as this may result in signal disconnection.

During the operation, a systematic approach to IONM assists in identifying the mechanism of nerve injury. Now advocated by many IONM practitioners, a four-step (V1/R1/R2/V2) procedure for systematic IONM was first described by Chiang and colleagues in 2008 [15]. The V1 EMG signal is first elicited through direct stimulation of the infrahyoid or sternocleidomastoid muscle and the vagus nerve itself. This second component may be accomplished through a small incision through the carotid sheath followed by direct stimulation with a sequence of small, 1–2 mA pulses at an event threshold of 100 μV [16]. Inability to elicit a V1 signal implies either equipment malfunction or a neural pathway that is not intact prior to dissection. Next, the R1 signal is obtained by mapping the RLN within the tracheoesophageal groove. Inability to elicit an R1 signal implies nerve injury during lateral dissection. Once the RLN is fully dissected, the proximal-most exposed portion is recorded as the R2 signal, and stimulation is reduced to 1 mA for the remainder of the case. A further reduction in amplitude may be necessary when branches of the recurrent laryngeal nerve are encountered. Reduced or absent R2 signal relative to R1 implies nerve injury during dissection. At the completion of all dissection and hemostatic maneuvers, and before operative closure or contralateral dissection, a final check of the vagus nerve should be performed (V2). When an impaired R2 or V2 signal is encountered, serial stimulation of the RLN starting from its distal-most portion at the laryngeal entrance and proceeding proximally can identify the point of nerve disruption. Notably, some experienced surgeons do not use this full sequence of maneuvers, in particular believing that routine entry into the carotid sheath solely for the purpose of IONM may be unnecessarily invasive.

A review of the literature and the cumulative experience of the International Neural Monitoring Study Group spanning nearly 15 years were reported by Randolph and colleagues in 2010. This group generated standards of practice for IONM. Noting that there is little uniformity in the practice of IONM and postoperative vocal cord assessment across many centers in the United States, the report was designed to establish standards and reduce variations in technique. Focusing on the endotracheal electrode detection method, guidelines included equipment setup, intraoperative troubleshooting, and waveform interpretation [17].

Many of the IONM guidelines for RLN also apply to EBSLN neuro-monitoring, with several important caveats. The incidence of EBSLN injury is highly variable in the literature given the heterogeneity in assessment modalities, ranging from videostrobolaryngoscopy to subjective surveys such as the Voice Handicap Index-10 (VHI-10). Transiently impaired EMG findings may be present in as high as 58 % of thyroidectomy patients, while up to 4 % experience permanent injury [1, 2, 18]. Intraoperatively, EBSLN integrity is verified either through a cricothyroid twitch response or through electromyographic response recorded by surface electrodes on the endotracheal tube. While the cricothyroid twitch response is present in all patients with an intact EBSLN, the glottic waveform is present in only 70–80 % of uninjured patients [19]. Technical recommendations for EBSLN neuro-monitoring were generated by the International Neural Monitoring Study Group in 2013, emphasizing two critical steps: (1) identifying the EBSLN via a positive cricothyroid twitch response (true positive) and (2) verifying a negative twitch response in the pedicle to be divided (true negative) [20]. Following this consensus, EBSLN and RLN guidelines will allow IONM newcomers to avoid many common technical pitfalls.

Troubleshooting

Given IONM's potential impact on intraoperative decision-making, the finding of loss of signal (LOS) should be approached methodically. Upon noting an absence of EMG activity or amplitude lower than 100 μV during RLN stimulation, a simple initial step to differentiate equipment malfunction from potential RLN injury is the laryngeal twitch test. This is performed by palpating the cricoarytenoid muscle posterior to the cricoid cartilage and assessing contraction in response to

RLN stimulation. A positive twitch response indicates a detection malfunction, such as a malpositioned endotracheal tube. An absent twitch response prompts further interrogation. Absence of signal with direct muscle stimulation suggests inadequate stimulation current, a dislodged grounding electrode, a defective probe, or neuromuscular blockade. Absence of signal with contralateral vagal stimulation suggests endotracheal tube malpositioning. A dry operative field should be verified, and the potentially injured nerve uncovered of overlying soft tissue. A simple algorithm for LOS troubleshooting is presented in Fig. 4.5. After accounting for possible confounding factors, persistent LOS should alert the practitioner of a likely RLN injury.

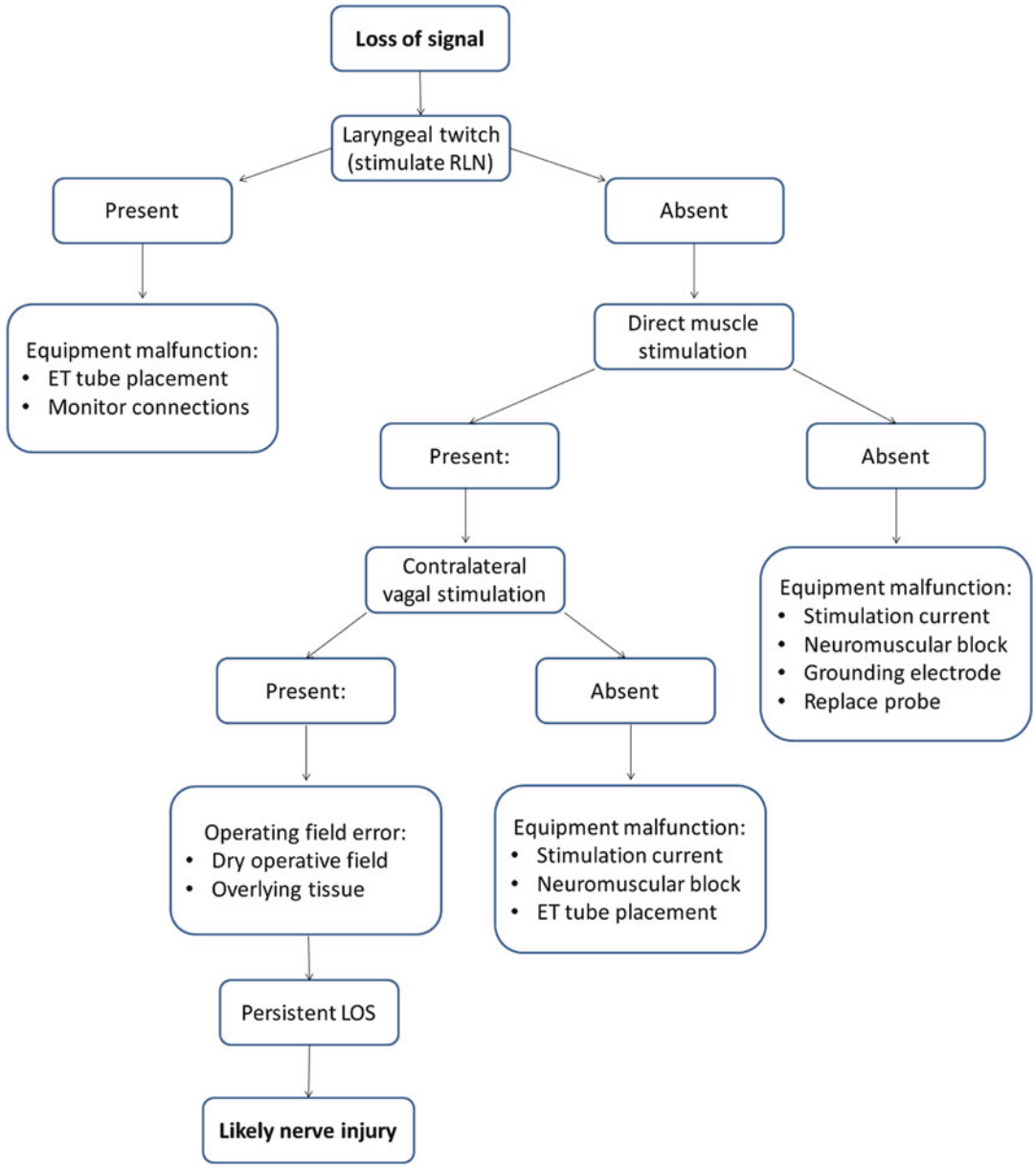

Fig. 4.5 Diagnostic algorithm for intraoperative neuro-monitoring with loss of signal

Outcomes of Neuro-monitoring

Electronic identification and monitoring of the RLN has been proposed by numerous reports as an adjunct to standard visual identification of the nerve during thyroid and parathyroid surgery. Interest in the expanding iterations of this technique has resulted in numerous reports suggesting its adoption and beneficial outcomes. Proponents contend that the device aids in the identification and preservation of the RLN, ultimately resulting in better outcomes including reductions in transient and permanent voice changes.

Laryngeal palpation as a means to intraoperatively assess RLN function was initially proposed in a series of 449 consecutive thyroid and parathyroid cases in which patients underwent pre- and postoperative laryngoscopy to assess vocal cord mobility [21]. A subset of patients underwent simultaneous laryngeal EMG recordings in addition to laryngeal palpation, and the two techniques were compared during intraoperative RLN stimulation. While no cases of permanent recurrent laryngeal paralysis were reported, one instance of temporary paralysis was correctly predicted by the absence of a palpable laryngeal twitch response.

Cernea and colleagues reported a prospective analysis of 447 thyroidectomy patients who underwent IONM with electrode-laden endotracheal tubes. Endoscopic vocal cord evaluation was performed on postoperative day 4 or 5 for all patients, and patients with vocal cord paralysis on early endoscopy underwent repeat video laryngoscopy after 4–6 months to assess long-term anatomic and functional changes [22]. Comparing primarily pre- and postoperative RLN stimulation (R1 vs R2) to vocal cord paralysis on endoscopy, the authors reported no false-negative results, a positive predictive value (PPV) of 40 %, and a negative predictive value (NPV) of 100 %. This suggested that a normal IONM result is highly effective in ruling out RLN injury at the end of an operation.

Barczynski reported in 2009 a randomized trial comparing thyroidectomy patients who underwent RLN visualization plus IONM versus visualization alone. There were 500 patients in each group, and indirect laryngoscopy was mandatory preoperatively and at day 2 postoperatively. Any patient showing nerve paresis was followed for a minimum of 12 months to assess for permanent damage. Reporting on both direct stimulation via the RLN and indirect stimulation of the vagus nerve, the authors noted superior accuracy through indirect stimulation, with an NPV of 98.9 % and a PPV of 37.8 %. Of note, 10 % of patients in the visualization-only group experienced transient or permanent nerve injury, a prevalence higher than most established reports. They concluded that nerve monitoring reduced the incidence of transient nerve damage by 2.9 %; however, permanent nerve damage was not statistically altered [23]. It is important to recognize that, due in part to the low rate of occurrence of RLN injury, these studies have in common high PPV and low NPV, indicating that IONM's primary utility lies in a normal reading's ability to rule out injury. Meanwhile, the clinical implications of an abnormal reading are less consistent.

While the aforementioned studies all highlight the potential prognostic value of IONM through early detection of nerve injuries, the therapeutic benefit of IONM is less commonly reported. Beldi reported results from 288 patients who underwent thyroid surgery with intraoperative nerve identification and IONM and reported a PPV of 33 % and an NPV of 99 %. While these values are comparable to Barczynski's group, Beldi's study noted no change in the incidence of nerve damage with adoption of IONM [24].

Dralle reported a prospective, non-randomized, multi-institutional study comprised of 16,448 consecutive operations, analyzing three treatment groups. Group 1 received no intraoperative nerve identification, Group 2 received visual nerve identification, and Group 3 received visualization plus intraoperative IONM via EMG. All patients underwent pre- and postoperative laryngoscopy. Across a variety of subgroup analyses based on thyroid pathology and provider volume, IONM demonstrated significant benefit over visualization alone only within the subgroup of patients

who underwent surgery for an immunogenic goiter. This group concluded that visual identification of the RLN was the gold standard of care and that IONM may have an adjunctive role in special cases as a "promising tool" for nerve identification and protection in extended thyroid resection procedures. Of note, this large collaboration reported important risk factors of permanent RLN paralysis, including recurrent goiters, thyroid malignancies, and lobectomies [25].

Snyder reported the utility of intraoperative nerve testing in 100 patients in a prospective registry of thyroidectomy and parathyroidectomy explorations. Reporting that IONM improved RLN localization 9.2 % of the time, they nevertheless noted a variety of means by which IONM falsely indicated injury (endotracheal tube rotation, wire disconnect, among others). Further, neither of the two nerve injuries that did occur were immediately identified using the neuromonitor. Thus, intraoperative monitoring did not effectively prevent RLN transection. This group concluded that nerve monitoring contributed most to early nerve identification in situations of anatomic variation or hazardous dissection by producing a positive signal, while a negative signal could indicate nonneural tissue, altered nerve function, or equipment malfunction [26]. In a recent follow-up report on 3435 nerves at risk which received IONM, the authors found that RLN identification increasingly relied upon nerve stimulation as experience with IONM accrued. Moreover, injury rate was lower among nerves initially identified by nerve stimulator. The group also noted a significant trend toward lower annual nerve injury rates during paratracheal lymph node dissection as experience with IONM increased. While no control group was assessed, the study nevertheless supports that IONM can provide useful, initial identification of the RLN in complex cases [27].

In a prospective study with a retrospective control group, de Pedro Netto reported their experience with 104 neuro-monitored patients. Video laryngoscopic examinations were performed on all patients preoperatively and up to 3 months postoperatively. They reported partial or total vocal cord mobility alterations at 3 months in 3.4 % of the nerves at risk. As was the case within the Snyder study, rotation of the electrode-laden endotracheal tube was the cause of a falsely negative signal in 4.8 % of patients. Comparing these results to a previous series of 100 patients with 3.1 % incidence of vocal fold mobility alterations, the authors reported no statistical difference in outcomes as a result of IONM [28].

Data from several large retrospective studies corroborate these prospective findings. In the largest single-institution study thus far, Calo and colleagues reported results from 2034 thyroidectomy patients, roughly half of whom were assigned IONM in a nonrandom fashion. Noting a 2.2 % injury rate among neuro-monitored patients and 2.8 % in unmonitored patients, the study showed no significant difference across the two groups despite high positive and negative predictive values of 77.8 % and 99.8 %, respectively. In recognizing that the study was inadequately powered to detect a difference in nerve injury rate, the authors identified a limitation that has thus far plagued all IONM research. They concluded that, while IONM may assist in nerve identification, it has not shown efficacy in reducing injury rate [29]. Shindo's group reported a medical chart review on 684 patients with over 1000 nerves at risk and showed that the incidence of unilateral vocal cord paresis was 2.1 % in the neuro-monitored group compared to 2.9 % in the unmonitored group. The difference was not statistically significant. The incidence of complete unilateral vocal cord paralysis was 1.6 % in each group. They concluded that monitoring the RLN during surgery did not appear to reduce the incidence of postoperative temporary or permanent complete vocal cord paralysis [30]. Chan reported their results with 647 consecutive patients undergoing thyroidectomy, representing 1000 nerves divided equally between a neuro-monitored group and a control group. No significant difference was noted in overall postoperative, transient, and permanent paralysis rates. However, within the control group, postoperative nerve palsy rate was higher among re-operative thyroidectomies. This pattern was not present in the IONM group. Therefore, although this report concluded that IONM during thyroid surgery

does not significantly affect overall RLN injury rate, the authors do advocate IONM for select high-risk thyroidectomies. For routine cases, visual identification and inspection of the nerve was endorsed as the appropriate intraoperative surgical strategy [31].

Additional, smaller retrospective studies have assessed IONM at single institutions but suffer from underpowered comparisons given the low observation rate of RLN injuries. Robertson reported a retrospective study of 165 patients undergoing thyroidectomy at a single academic institution. A control group was compared to a group which underwent IONM, and the overall rates showed no significant differences in RLN paralysis, paresis, or total injury rates. This pattern was present even among patients with advanced T stage and increased baseline risks [32]. In another review of 136 consecutive thyroid surgeries, Witt and colleagues compared 83 nerves which underwent monitoring to 107 nerves which did not, noting that IONM did not reduce the incidence of transient or permanent vocal fold immobility and that monitoring results did not always concur with postoperative vocal fold assessments. However, they did make the observation that monitoring may help document intraoperative anatomic integrity of the nerve if the patient should subsequently notice postoperative vocal fold disability [33].

In an effort to assess the incidence of subclinical minor injury to the RLN, Chiang reported a single surgeon experience using a four-step procedure by which EMG signals from the vagus and RLNs are assessed before and after thyroid resection. Out of 113 patients and 173 at-risk nerves, this technique identified 16 nerves which had altered postoperative EMG signals. It was felt that the majority of these represented minor stretch injuries occurring within the region of the ligament of Berry. The group came to the conclusion that, although the four-step IONM technique did not reduce the rate of the RLN injury, it did provide useful evidence to retrospectively identify when intraoperative over-manipulation of the nerve had occurred [34].

Recently, a systematic review with meta-analysis of studies comparing IONM of the RLN versus visualization alone during thyroidectomy has been reported [34]. Among the included data were three prospective randomized trials, seven prospective cohort studies, and ten retrospective observational studies. The report included 23,512 combined patients representing over 24,000 at-risk nerves in the IONM group and 11,400 at-risk nerves in the group receiving visualization alone. The rates of overall RLN palsy per at-risk nerve were 3.5 % in the monitored group and 3.7 % in the unmonitored group. Transient palsy rates were 2.6 % and 2.7 % in the monitored and unmonitored groups, respectively, while permanent palsy rates were 0.8 % and 0.9 %, respectively. None of these differences were statistically significant. Under subgroup analysis for patients at high risk for nerve injury, IONM similarly did not confer significant benefit to nerve palsy rate. Finally, the authors noted a nonsignificant trend toward longer operative time from incision to closure among neuro-monitored cases (97.6 vs 94.6 min).

As a relatively new option, there have been no randomized, prospective trials comparing continuous IONM to either visual identification or intermittent IONM. In a recent multicenter trial, Phelan and colleagues reported that continuous IONM in 102 thyroidectomies resulted in no nerve injury or other adverse events. Moreover, the authors defined two thresholds of signal abnormality: concordant amplitude reduction and latency increase (combined events) and loss of signal. Severe combined events were associated with reversible vocal cord paralysis and a low PPV (33 %), much like data from classic IONM. On the other hand, loss of signal occurred more infrequently and indicated severe and likely irreversible injury, with a PPV of 83 % [35]. These data argue for continuous IONM's role in providing early warning to the surgeon with the goal of modifying surgical approaches prior to irreversible injury. This potential advantage will require verification through prospective comparative study and must be weighed against the increased invasiveness of continuous vagal efferent stimulation. While no adverse events have been reported thus far, there are data demonstrating unbal-

anced parasympathetic escalation in small patient samples [36].

Neuro-monitoring for EBSLN was described in 2000 by Jonas and colleagues, who were able to identify 38 % of at-risk nerves in 108 patients [3]. This early study did not employ extensive proximal dissection with the purpose of identifying the EBSLN; subsequent reports have reported identification rates greater than 80 % [19, 37]. In a randomized trial of IONM versus visualization for thyroidectomies under local/regional anesthesia, Lifante and colleagues compared VHI-10 outcomes pre- and postoperatively. Both groups had higher VHI-10 scores at 3 weeks postoperatively compared to preoperative values, consistent with the high incidence of transient EBSLN injury. However, patients in the IONM group recovered preoperative VHI-10 performance on 3-month follow-up, while visualization-only patients had persistently elevated index scores [38]. Objective videostrobolaryngoscopy and functional voice assessments were not reported in this trial, but results indicated a potential role for EBSLN neuro-monitoring.

Barczynski and colleagues conducted a randomized, single-blinded study comparing IONM using endotracheal surface electrodes to visualization alone in the setting of general anesthesia [19]. Objective and subjective criteria were used, including videostrobolaryngoscopy and functional voice assessments at 2–3 weeks and 3 months following surgery. The group reported higher rates of impairment detected by both modalities at the 2–3 week time point; however, performance at 3 months following surgery was similar between groups. Of note, the authors reported 3/105 false-positive findings, in which signal was lost following resection in the setting of an anatomically intact nerve. Data from a meta-analysis by Sanabria and colleagues collaborate these findings, indicating that while neuro-monitoring does increase the rate of EBSLN identification (69 % vs 29 % of at-risk nerves), it is not associated with a significant reduction in the rate of definitive palsy compared to visualization alone (0.3 % vs 0.9 %) [39].

Considerations for the Use of Intraoperative Neuro-monitoring

Despite a paucity of convincing data demonstrating that IONM reduces the risks of clinically meaningful RLN injury or results in better vocal cord functional outcomes, considerations may be made in its defense as an adjunct to nerve visualization.

Definition of Anatomy

IONM may help define the anatomy of the operative field in the setting of anomalous laryngeal nerve anatomy. IONM can alert the surgeon to rare nonrecurrent laryngeal nerves early by projecting an abnormal, short-latency waveform when the vagus nerve is stimulated. In cases of bifurcated RLNs, IONM with or without intraoperative palpation for a cricoid muscle response may help delineate the anterior branch of bifid nerves, thereby avoiding injury to motor function.

IONM might also be used in a subset of patients whose presenting anatomy, diagnosis, or previous operative history offers significant intraoperative challenges. Unsurprisingly, the definition of "risky anatomy" varies across published reports. Chan et al. defined patients undergoing re-operative surgery or carrying a diagnosis of thyroid cancer, toxic goiter, or retrosternal extension as being more "high risk." As mentioned above, this study provided data which support the use of IONM among re-operative patients [31]. Hermann evaluated 328 patients (a total of 502 nerves at risk) using IONM, stratifying operations for malignant disease and reoperations as a high-risk subgroup. The authors noted that IONM was poorly sensitive to injury within this high-risk subgroup (<60 %) compared to benign primary operations (86 %). However, negative predictive value was excellent among all patients; therefore, the authors ultimately endorsed IONM for cancer or re-operative surgery [40]. Sanabria raises the point that careful review of the litera-

ture is appropriate in the definition of "high risk" as definitions may vary from author to author [39]. While most studies classify patients with one risk factor as "high risk," the contribution of individual risk factors to clinical outcome is unclear, and there is no broadly accepted risk classification for thyroid surgery. While some patient variables such as re-operation, cancer, and goiter are frequently reported as relevant risk factors, others (preoperative palsy, lymph node dissection) are inconsistently considered. As a result, the true prevalence of "high-risk" patients for which IONM may be beneficial is unknown.

For straightforward cases in which aberrant RLN anatomy is not expected, the primary role of neuro-monitoring may be as an instructive tool. Implementation in this setting can also allow providers to gain familiarity with using the device and interpreting its output. For a minority of more complex cases, the presence of high-risk anatomy—as a result of re-operation, cancer invasion, or extensive goiter—may warrant IONM as an adjunct to visual inspection by defining the anatomy of the nerve and verifying its integrity during dissection and at the end of the operation.

Surgeon Experience

Another area of consideration is the selective use of IONM based on surgeon experience. While it may be the case that only experienced providers have adequate patient volume to realize a benefit from IONM, it is well documented that high-volume surgeons also tend to have a relatively low rate of RLN injury [41]. Therefore, among these providers, a prohibitively large number of patients would be needed in order to adequately power a study that can test the benefit of IONM. On the other hand, given its ability to delineate difficult or anomalous anatomy, IONM may be expected to have more noticeable utility among inexperienced surgeons. However, there is a paucity of data supporting this hypothesis in the current literature. Dralle's report on nearly 30,000 nerves at risk showed that medium-volume centers (90–275 nerves per year) tended to have higher rates of RLN injury compared to low- and high-volume centers. However, even within these centers, IONM failed to significantly reduce the rate of injury [25].

In a survey of The American Association of Endocrine Surgeons reported by Sturgeon and colleagues, the overall prevalence of IONM use (either routine or selective) was 37 % among society members. Nearly 50 % of high-volume surgeons (≥100 operations per year) reported that they used IONM compared to 22 % of low-volume surgeons. Overall, 76 % of respondents answered that IONM does not improve thyroid surgery safety, including 56 % of IONM users. Sanabria and others have warned that neuro-monitoring should never replace diligent dissection and direct visualization of the RLN, as the novice surgeon may erroneously interpret IONM outputs and develop a false sense of security [42].

Intraoperative Decision-Making

A third potentially useful contribution of IONM is toward intraoperative decision-making. Goretzki retrospectively evaluated the use of IONM among 1333 consecutive patients who underwent thyroid surgery for suspected benign bilateral thyroid disease. They studied how intraoperative pathologic IONM findings on the initial side of thyroid resection affected subsequent operative proceedings on the opposite side. Preexisting or directly visible damage to the nerve on the initial side of dissection was reported in 13 patients. In 11 of these cases, surgical strategy was changed by restricting further dissection or by calling in a more experienced surgeon. Among 36 operations with pathologic IONM findings on the initial side of dissection, 20 underwent a similar change in surgical strategy. Of the 16 operations which continued unaltered, 3 culminated in bilateral vocal cord paralysis. Two of these cases proceeded due to normal IONM results despite the fact that injury had occurred. In their series, there was a 17 % chance of bilateral RLN damage when surgeons were not aware of a preexisting or highly likely nerve injury. Data from this report reflect both sides of

the IONM debate. Although IONM can impact intraoperative decision-making by indicating nerve injury on the initial side of dissection, falsely normal results can mislead surgeons into continuing resection on the opposing side [43]. Sadowski and colleagues corroborated these findings in a study of 220 bilateral thyroidectomies, citing 9 cases for which intraoperative findings of IONM signal loss on the initial side of resection resulted in termination of the operation. Within this series, the PPV was 78 % [44].

The sensitivity of IONM for RLN injury has been variably reported to be between 60 % and 95 %. The positive predictive value of the technique is similarly inconsistent (30–80 %). This makes decision-making difficult when a signal loss occurs and there is no visible damage to the integrity of the RLN. For obvious reasons, there is a paucity of published data on the outcomes of bilateral complete thyroidectomy in the setting of suspected unilateral RLN injury by IONM. However, the practice has been described, typically in the practice of highly experienced specialists [45].

Definition of Outcomes

Over the last decade, quality metrics are increasingly scrutinized in surgical practice. As a result, there is growing interest in objective measures of surgical outcomes. In the setting of thyroid surgery, few would argue that preservation of normal or minimally damaged voice control is one of the primary quality indicators outside of the adequacy of resection margins. Other parameters include avoidance of hypoparathyroidism and wound infections. Interestingly, objective measures of vocal cord function such as direct or fiber-optic laryngoscopy and videostroboscopy do not always correlate with voice control function. Especially during the early postoperative course, endotracheal intubation can confound patients' abilities to self-assess voice control. In a recent study of 100 thyroidectomy patients, de Pedro Netto reported subjective voice changes in 30 % of patients with normal vocal fold mobility on videolaryngoscopy [46].

Not surprisingly, the relationship between IONM findings and clinically relevant voice function is unclear. Due in part to the high rate of transient vocal abnormalities after intubation, most IONM studies use laryngoscopy as the gold-standard assessment of vocal fold function. In a recent study of 244 patients with known preoperative vocal cord paralysis, 17 % had a normal IONM signal on the paralyzed side, indicating an imperfect correlation between objective signals and clinical function [45]. Nevertheless, given its status as the only widespread method for intraoperative vocal cord assessment and its potential impact on operative decision-making, it is conceivable that routine implementation of IONM may eventually become a process-based quality measure in thyroid surgery. In anticipation of this, an argument may be made for the early adoption of IONM—particularly within lower-volume centers—in order to gain familiarity with the tool's advantages and pitfalls.

Cost-effectiveness

There are few articles that discuss the cost-effectiveness of IONM. Equipment costs associated with IONM necessarily vary according to the detection strategy used. While the vocal cord palpation method requires only the fixed cost of the IONM stimulator and output display, the most common method—endotracheal electrode electromyography—requires flexible costs associated with each specialized endotracheal tube. Studies by Hemmerling [47] and Dionigi [48] both allude to minimal costs of implementation. However, both authors recommend that the precise placement of the endotracheal tube electrodes over the vocal folds should be documented through fiber-optic laryngoscopy, thereby adding unmeasured costs to both operative time and equipment. Furthermore, there are no studies in the literature accounting for costs of delayed reoperation in the case of false-positive outcomes or the cost of nerve palsy treatment in the case of true positives. It is reasonable to consider that the expense of the technology may represent only a

small proportion of the total cost of the procedure; to date, a decision analysis accounting for direct and indirect costs and utilities has not been performed. Such a study will need to include thoughtful sensitivity analyses to account for contributions to injury risk originating from the patient, the disease pathology, the operation, and the operating surgeon.

Conclusions

Taking the literature in aggregate, we consider direct anatomic identification and protection of the recurrent laryngeal nerve to be the gold standard. IONM is an increasingly popular adjunctive tool among thyroid and parathyroid surgeons. Currently, data on clinically meaningful benefit over anatomic nerve visualization alone are lacking. This is secondary to a number of factors, including the variable accuracy of IONM across the literature and the overall low incidence of RLN injury. We believe that experienced surgeons are unlikely to notice a measurable clinical benefit from implementing IONM on a routine basis. Even in the setting of re-operations and other high-risk procedures, any measurable change in clinical outcomes will require thousands of operations to materialize. Nevertheless, there is evidence that IONM can serve as a useful instructive tool, help delineate complex anatomy, and affect intraoperative decision-making. Therefore, surgical trainees should be encouraged to become familiar with IONM in order to make informed decisions regarding its implementation. Only by gaining practical experience with this technology can surgeons acquire competency regarding its utility, limitations, and pitfalls.

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Who Should Do Thyroid Surgery?

5

Tracy S. Wang and Julie Ann Sosa

The earliest accounts of thyroid surgery, reported in the twelfth and thirteenth centuries AD, describe the use of setons, hot irons, and caustic powders, often with fatal results, which ultimately impeded further attempts at thyroid surgery for several centuries. In the late nineteenth century, the American surgeon Samuel Gross described thyroid surgery as "horrid butchery" that "no honest and sensible surgeon would ever engage in…" [1]. Nonetheless, several premier surgeons of the nineteenth and early twentieth centuries made landmark strides in the safety of thyroid surgery. Theodor Billroth had an initial mortality rate of 40 % after his first 20 thyroidectomies; however, by the end of his career, he had become one of the most experienced thyroid surgeons in the world, reporting a mortality rate below 8 %. Improvement in surgical instrumentation and the introduction of antiseptics and anesthesia also clearly enhanced patient outcomes over this time period. Similarly, Theodor Kocher had an initial mortality rate of 12.8 % after his first 100 thyroidectomies; by 1917, several weeks before his death, he reported an overall mortality rate of 0.5 % from approximately 5000 thyroidectomies performed [1].

These early experiences are some of the best anecdotal evidences for a relationship between surgeon volume and patient outcomes. Over the past decade, numerous population-based studies have demonstrated the strong association between clinical and economic outcomes from surgical procedures and hospital volume; this "volume–outcomes" relationship has been the strongest for cardiovascular operations (abdominal aortic aneurysm repair and coronary artery bypass graft surgery) and major cancer resections (including pancreatic and esophageal resections) but have also included procedures in bariatric and endocrine surgery [2–6]. However, recent studies also have shown an association between patient outcomes and surgeon experience/volume, independent of hospital volume [7, 8]. A recent study of Medicare claims data demonstrated that surgeon volume was inversely related to operative mortality in eight cardiovascular and oncologic procedures. Moreover, the apparent effect of hospital volume could be attributed to surgeon volume; high-volume surgeons had lower mortality rates than low-volume surgeons, irrespective of the surgical volume of the hospital [6]. These

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findings of improved patient outcomes in the hands of high-volume surgeons are borne out within endocrine surgery, a surgical specialty typically associated with low mortality rates and where measurement of postoperative complications is more pertinent. In multiple studies, on average, patients of high-volume surgeons have been shown to have lower complication rates and shorter hospital length of stay [9–13].

This chapter will review the current literature on the relationship between surgical volume and patient outcomes in thyroid surgery, examining both provider characteristics (surgical training and specialty) and the effects of experience on patient outcomes, particularly in vulnerable populations, as defined by age, race, and socioeconomic status.

Surgeon Volume and Experience

In the earliest study examining the effects of individual surgeon experience on short-term clinical and economic outcomes for thyroidectomy, Sosa et al. performed a cross-sectional analysis of 5860 patients undergoing thyroidectomy in a single state over a 6-year period (1991–1996) and categorized 658 surgeons by total volume of cases over the study period, 1–9 cases, 10–29 cases, 30–100 cases, and >100 cases [9]. Overall, nearly two-thirds of surgeons performed <1 thyroidectomy per year, on average, and the median number of thyroidectomies was 25 (range, 4–98). On both unadjusted and adjusted analyses, the highest-volume surgeons had the lowest complication rate ($p<0.001$), the shortest hospital stay ($p<0.05$), and the lowest hospital charges compared with all other surgeons (Table 5.1). In a subgroup analysis of surgeons with operating privileges at >1 hospital, patient's length of stay was associated with surgeon volume, not hospital volume. The authors found that >20 % of complications and 1700 hospital days could have been prevented/saved if high-volume surgeons had performed all thyroidectomies [9].

Subsequent population-based studies also have demonstrated this association between surgeon volume and patient outcomes. Stavrakis et al. utilized discharge data from a single year (2002) from two states (New York and Florida) [10]. Surgeons were divided into five groups, based on annual surgical volume (1–3, 4–9, 9–19, 20–50, 51–99, and ≥100 cases). Expected complication rates were generated to estimate the probability of complications for each patient, and the predicted probabilities were then summed to arrive at the expected number of complications for each surgeon volume group. A ratio of observed/expected (O/E) complication rates was then calculated. For thyroidectomy, surgeons performing 1–3 cases per year had a disproportionately high number of complications (O/E, 1.36; $p<0.02$), while those performing ≥100 cases annually had a disproportionately low number of complications (O/E, 0.65; $p<0.10$). Surgeon volume also was inversely correlated with the risk of postoperative hemorrhage, and each unit increase in thyroidectomy volume was associated with a 0.06-day decrease in length of stay ($p<0.0001$) and a $365 (2002 US dollars) decrease in total costs ($p<0.001$) [10].

In a study of discharge data from the Health Care Utilization Project Nationwide Inpatient Sample (HCUP–NIS) of 871,644 patients who

Table 5.1 Unadjusted and adjusted clinical and economic outcomes from thyroidectomy by surgeon volume group

Outcomes	Surgeon volume groups			
	1–9 cases	10–29 cases	30–100 cases	>100 cases
Complication rate				
Unadjusted (%)	10.1	6.7	6.9	5.9
Adjusted (%)[a]	8.6	6.1	6.1	5.1
Length of stay				
Unadjusted (days)	2.8	2.1	2.2	1.7
Adjusted (days)[a]	1.9	1.7	1.7	1.4
Hospital charges				
Unadjusted ($)[b]	5078	4084	4016	4777
Adjusted ($)	3901	3693	3585	3950

[a]Adjusted for patient age, race, comorbidities, insurance status, diagnosis, procedure, surgeon, and hospital volume
[b]1996 United States dollars
Reprinted with permission from Sosa et al. The importance of surgeon experience for clinical and economic outcomes from thyroidectomy. Ann Surg 1998;228(3):320–330

underwent thyroid surgery between 1993 and 2008, individual surgeon and individual hospital annual thyroid surgery volumes were studied. Surgeon thresholds for volume were defined as very low (≤3 cases per year), low (4–9), intermediate (9–23), and high (>23); a higher threshold for surgeon volume (i.e., >100 cases) was not used as in previous studies, as this was found to represent only surgeons in the 98th percentile for volume. Hospital thresholds for volume were defined as very low (≤25 cases per year), low (26–42), intermediate (43–76), and high (>76). High-volume surgeons had a lower incidence of endocrine-specific complications, such as recurrent laryngeal nerve injury (OR = 0.7; $p = 0.024$) and hypocalcemia (OR = 0.07; $p = 0.002$); after adjustment for surgeon volume, having a procedure performed at a high-volume hospital was not associated with postoperative morbidity [13].

Surgical Volume and Patient Outcomes, By Race

Racial disparities in healthcare are well documented, with racial and/or ethnic minorities having less access to preventative care and to surgery, possibly resulting in delayed diagnoses and more advanced disease at presentation [14, 15]. Using the HCUP–NIS, a stratified 20 % sample of inpatient admissions to acute care hospitals nationwide and the largest all-payer inpatient database in the United States, Sosa et al. reviewed 16,878 adult patients undergoing thyroidectomy in 2003–2004 [16]. The majority of the patients were white (71 %); the remaining patients were black (14 %), Hispanic (9 %), and other (6 %). Overall, black patients had the highest percentage (3.7 %) of all patients in the "major and extreme loss of function" category postoperatively, and they had significantly longer mean length of stay (2.5 days) compared to Hispanic (2.2 days) or white (1.8 days) patients ($p < 0.001$). Blacks also had higher overall complication rates compared to whites or Hispanics (4.9 % vs. 3.8 % vs. 3.6 %, respectively), an observation that approached statistical significance on univariate analysis but that did not remain so on multivariate analysis. Surgeons were grouped by annual case volume, with the lowest-volume surgeons performing 1–9 cases per year and the highest-volume surgeons performing >100 cases per year. Not only did the majority of Hispanic (55 %), other (53 %), and black (52 %) patients have surgery by the lowest-volume surgeons, compared to 44 % of white patients, but a higher proportion of white patients had surgery performed by the highest-volume surgeons (7 %), compared to 2 % of blacks and 1 % of Hispanics [16].

A more recent study also utilized the HCUP–NIS database to examine the association between surgical volume and racial disparities between 2003 and 2009, although the authors included patients undergoing both thyroid and parathyroid surgeries [17]. Still, the conclusions were similar, in that higher surgeon volume was associated with improved patient outcomes. Individual surgeon volume was available for 9352 surgeons performing 63,264 procedures; these surgeons were divided into three groups, based on the number of procedures performed over the 7-year study period: low (<10 cases), intermediate (10–99 cases), and high volume (≥100 cases). These authors also found a difference in access to surgeon volume according to racial groups, with access to high-volume surgeons being the highest among Asians (24 %), followed by whites (19 %), blacks (16 %), and Hispanics (13 %); $p < 0.001$). For all racial groups, surgeons with the highest volume had the fewest number of complications and shortest length of stay on both univariate and multivariate analyses [17].

Surgical Volume and Patient Outcomes, By Age

The Elderly

The prevalence of thyroid disease increases with age, and multiple risk stratification systems, including AGES (age, grade, extent, size), AMES (age, metastases, extent, size), and the American Joint Committee on Cancer (AJCC) staging systems, use an age threshold of >45 years for patients who are at higher risk of disease recurrence and death from thyroid cancer [18, 19].

While older patients have been shown to have higher rates of perioperative morbidity and mortality associated with many procedures, there is conflicting data on whether thyroidectomy can be performed among the elderly without an associated increase in morbidity or mortality [20–22].

In several single-provider and single-institution series, there have been conflicting data on the outcomes of elderly patients following thyroid surgery [21–25]. Mekel et al. reviewed a single institution's experience with 3568 patients undergoing thyroidectomy; 90 patients ≥80 years were compared with a cohort of 242 randomly selected patients between 18 and 79 years [22]. The octogenarians had a higher mean Charlson comorbidity index (mean 1.08 ± 1.38 vs. 0.38 ± 0.89; $p < 0.001$) and a significantly longer mean length of stay (1.7 ± 2.2 days vs. 1.2 ± 2.9 days; $p < 0.001$). Overall complication rates also were higher among the octogenarians (24 %) than among the younger cohort (9 %; $p < 0.001$); thyroidectomy-related complication rates also were higher for the octogenarians (5.5 % vs. 2.5 %; $p < 0.001$). However, on multivariate analysis, patient age was not an independent risk factor for complications (OR, 1.899; 95 % confidence interval, 0.803–4.489) [22].

Other population-based studies have shown that elderly patients are indeed at higher risk for complications after thyroid surgery. Grogan et al. utilized the American College of Surgeons (ACS) National Surgical Quality Improvement Program (NSQIP) database from 2005 to 2008 to examine the outcomes of patients undergoing thyroidectomy [23]. Patients were divided into three age groups: young (16–64 years), elderly (65–79 years), and super-elderly (≥80 years). Outcomes were aggregated into the following categories: urinary tract infection, wound infection, systemic infection, cardiac complications, pulmonary complications, and 30-day mortality; endocrine-specific complications of recurrent laryngeal nerve injury or hypoparathyroidism were not discretely coded in NSQIP, limiting the current utility of this database for addressing thyroidectomy-based questions. Overall, the complication rates were lowest for the young (1.0 %), followed by the elderly (2.2 %) and super-elderly (5.0 %); when plotted by 5-year age increments, the elderly had a 112 % increased risk of complications compared to the young, and the super-elderly had a 388 % increased risk of complications. Hospital length of stay also was significantly longer for the elderly (1.4 days) and super-elderly (1.8 days) compared to the young (1.1 days). On multivariate regression analysis, age >65 years was an independent risk factor for postoperative complications in thyroidectomy patients ($p < 0.01$) [23].

In a study utilizing SEER–Medicare, 2127 patients >65 years (mean age, 74 years) who underwent thyroidectomy between 1997 and 2002 were studied to predict the risk of rehospitalization [24]. Within 30 days of discharge after thyroidectomy, 171 (8 %) patients underwent 185 unplanned rehospitalizations; these patients had significantly higher Charlson comorbidity index scores, advanced stage of disease, and longer mean hospital length of stay compared to younger patients at the time of initial surgery (2.8 vs. 1.8 days, respectively). The most common cause of an unplanned readmission was endocrine related (hypocalcemia/hypoparathyroidism), and patients with endocrine-specific complications were more likely to be readmitted than patients whose complications were not endocrine specific (17 % vs. 7 %; $p < 0.001$). The mean length of stay of an unplanned rehospitalization was 3.5 days, with a mean cost of $5921. An unplanned rehospitalization also was associated with death at 1 year after surgery (18 % vs. 6 % if there was no rehospitalization; $p < 0.001$) [24].

In a study using data from 2003 to 2004 in HCUP–NIS, Sosa et al. examined the outcomes of 22,848 patients undergoing thyroidectomy; this included 4092 (18 %) patients aged 65–79 years and 744 (3 %) patients ≥80 years [25]. For the entire cohort of patients, the highest-volume surgeons (>100 thyroidectomies/year) had shorter length of stay and complication rates than lower-volume surgeons. In spite of this, the lowest-volume surgeons (1–9 thyroidectomies/year) did the largest share of thyroidectomies for all groups, operating on 52 % of patients aged 65–79 years and 58 % of patients ≥80 years, compared with 47 % of patients 18–44 years and

46 % of patients 45–64 years ($p<0.001$). Surgeons performing ≥30 thyroidectomies per year performed only 23 % of thyroidectomies in patients aged 65–79 years and <16 % thyroidectomies in patients ≥80 years ($p<0.001$) [25].

Older patients were more likely to undergo substernal thyroidectomy and had more comorbidities based on their Charlson comorbidity index, differences which appeared to be associated with differences in clinical and economic outcomes, as seen in previous studies. In a subgroup analysis of patients ≥65 years, the average length of stay for octogenarians was 2.9 days, compared to 2.2 days for patients 65–79 years ($p<0.001$); complication rates also were higher (5.6 % vs. 2.1 %; $p<0.001$). Importantly, procedures performed by high-volume surgeons had a shorter length of stay (2.3 vs. 4.8 days) and lower complication rates (4.5 % vs. 13 %) than those by lower-volume surgeons [25]. After stratifying for patient age and comorbidity (0–2 vs. ≥3 comorbidities), outcomes in patients 65–79 years and ≥80 years were examined based on annual surgeon volume (low volume 1–29 cases; high volume ≥30 cases). In this analysis, the higher-volume surgeons had shorter length of stay (2.2 vs. 7.7 days) and lower complication rates (11 % vs. 25 %) (Fig. 5.1) [25].

Pediatrics

Healthcare disparities and access to high-quality healthcare have been well documented in the pediatric population [26, 27]. This is important in the management of pediatric patients with thyroid disease because although thyroid nodules are uncommon in children (patients ≤18 years), when present, there is a fivefold greater risk that a malignancy will be diagnosed in the nodules compared to adults. Indeed, thyroid cancer is the most common cancer in pediatric patients [28, 29]. In addition, Graves' disease is the most common cause of pediatric hyperthyroidism, and there remains controversy regarding whether optimal treatment modality is surgery or radioactive iodine. Proponents of surgery cite the high cure rates and low complication rates after thyroidectomy, even in the pediatric population [30].

In a population-based study using HCUP–NIS data from 1999 to 2004, outcomes of 1199 children (defined in this study as <18 years) undergoing thyroidectomy and parathyroidectomy were evaluated; the majority (1094 patients; 91 %) underwent thyroid surgery [31]. Children had higher rates of endocrine-specific complications than adult patients (9.1 % vs. 6.3 %; $p<0.001$);

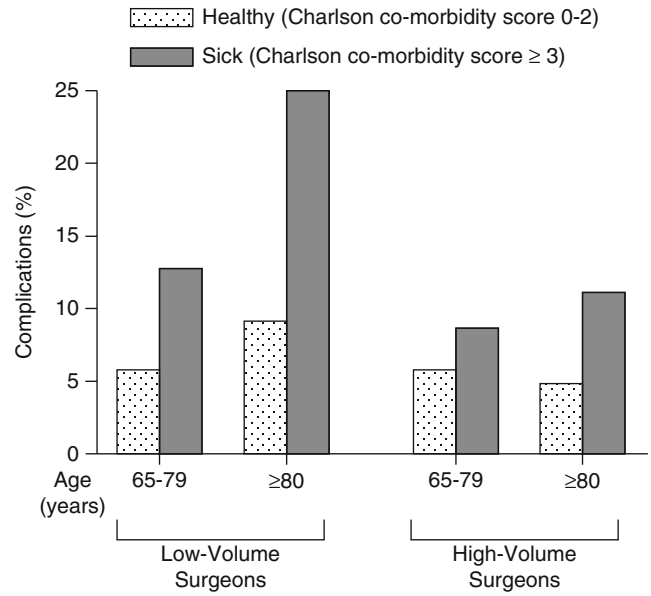

Fig. 5.1 Thyroidectomy complications for patients ≥65 years, by comorbidity and surgeon volume. Reprinted with permission from Sosa et al. A population-based study of outcomes from thyroidectomy in aging Americans: At what cost? J Am Coll Surg 2008; 206: 1097–1105

this included a rate of 68.6 % for postoperative hypocalcemia. In particular, hypocalcemia was significantly higher in children (9.3 %) compared to adults (5.7 %; $p<0.01$). Overall complication rates also were higher for the youngest children (0–6 years; 22 %) compared to children 7–12 years (15 %) and 13–17 years (11 %; $p<0.01$). Specifically, recurrent laryngeal nerve-related injuries were also the highest for the 0–6 year group (3.8 %); this rate decreased to 1.1 % in children aged 7–12 years and 0.6 % in children aged 13–17 years ($p<0.05$) [29].

Tuggle et al. performed an analysis of the relationship between surgeon volume and outcomes in 607 pediatric patients undergoing thyroidectomy and parathyroidectomy using HCUP–NIS [32]. In this study, surgeons performing >30 cervical endocrine procedures per year in adults and children were defined as high volume; these surgeons performed an average of 72 pediatric and adult endocrine procedures per year (range, 31–183). Pediatric surgeons were identified as those surgeons restricting >90 % of their practices to patients ≤17 years, and they performed an average of two pediatric endocrine procedures per year (range, 1–8). High surgeon volume was associated with better patient outcomes, with endocrine-specific complication rates of 5.6 %, compared with 11.0 % for pediatric surgeons and 9.5 % for all other surgeons (Table 5.2). High-volume surgeons also had significantly shorter length of stay (1.5 days), compared to 2.3 days for pediatric surgeons and 2.0 days for other surgeons ($p<0.05$), and lower inpatient costs ($12,474 vs. $19,594 for pediatric surgeons and $13,614 for other surgeons; $p<0.01$). Surgeon volume was an independent predictor of length of stay and cost, and surgeon specialty was not associated with outcomes in multivariate analysis. These results suggest that the most important predictor of pediatric outcomes after cervical endocrine surgery is surgeon volume, not surgeon specialty, and that the best outcomes are achieved by surgeon experience in both adult and pediatric thyroid disease [30].

There are data to support that a collaborative surgical approach may be appropriate for pediatric thyroidectomy [33]. Wood et al. describe their institutional experience with pediatric thyroid surgery, in which operations are performed at a children's hospital by both a pediatric surgeon and an endocrine surgeon. Of the 35 children undergoing thyroidectomy, the overall median length of stay was 1 day (range, 0–8); no patient had a recurrent laryngeal nerve injury or hematoma, and four (8.9 %) patients had postoperative hypocalcemia, although all were transient (requiring calcium supplementation for <6 months). This collaborative approach toward pediatric endocrine surgery also has been endorsed by the American Thyroid Association in recent guidelines for the management of pediatric thyroid cancer; with a recommendation rating of "B" (recommends, based on fair evidence), the guidelines state that "Pediatric thyroid surgery should be performed in a hospi-

Table 5.2 Unadjusted clinical and economic outcomes after pediatric thyroid and parathyroid procedures by surgeon volume and specialty (otolaryngology–head and neck surgeons [OHNS] vs. general surgeons), 1999–2005 ($n=607$)

	High volume				Low volume				
	All high volume	OHNS ($n=28$)	General ($n=98$)	p	All low volume	OHNS ($n=93$)	General ($n=388$)	p	High vs. low volume
Complications (%)									
General	8.7	14.3	7.1	NS[a]	13.3	17.2	12.4	NS	NS
Endocrine	5.6	10.7	4.1	NS	10.0	14.0	9.0	NS	NS
Length of stay (days)	1.5	1.7	1.5	NS	2.1	2.5	2.0	NS	<0.05
Cost (2005 US$)	12,474	12,931	12,346	NS	15,662	16,091	15,558	NS	<0.05

[a]*NS* not significant

Reprinted with permission from Tuggle et al. Pediatric endocrine surgery: Who is operating on our children? Surgery 2008; 144: 869–877

tal with the full spectrum of pediatric specialty care, to include, but not be limited to … a high volume thyroid surgeon…" and that "pediatric thyroid surgery should be performed by a surgeon who performs at least 30 or more cervical endocrine procedures annually… thyroid surgery performed under these guidelines is associated with lower complication rates, decreased hospital stay, and lower cost" [29].

Surgical Training and Specialty

The role of surgical training and specialty in the outcomes of patients undergoing thyroid surgery has been much discussed, with both a focus on surgeon volume and patient outcomes, as well as the proliferation of endocrine surgery fellowships. In a study utilizing data from the Accreditation Council for Graduate Medical Education, a survey of American Association of Endocrine Surgeons, and the HCUP–NIS, it was reported that graduating general surgery chief residents performed, on average, <30 endocrine procedures during training, including on average just 18 thyroidectomies. In contrast, graduates of endocrine surgery fellowships performed on average 253 endocrine procedures, including 127 thyroidectomies [34]. Zarebczan et al. utilized records from the Resident Statistic Summaries of the Residency Review Committee for general surgery and otolaryngology residents between 2004 and 2008 [35]. During this time, general surgery residents increased their mean case volume from 26.4 to 30.9 cases, including an increase in thyroidectomy cases from a mean of 18–22 cases ($p=0.007$), while otolaryngology residents saw an increase from 57 to 67 cases, including an increase from 47 to 54 thyroidectomies ($p=0.04$) [35]. These data lend further insight to answering the question of whether graduates of general surgery residency programs have adequate exposure to endocrine surgery during their 5 years of training to safely perform thyroidectomy at the time of graduation, without fellowship.

Other studies have shown that surgeon specialty plays less of a role in patient outcomes than surgeon volume [32, 33, 36, 37]. The studies described previously by Tuggle et al. and Wood et al. on the outcomes of pediatric thyroidectomy also support the tenet that surgeon volume remains a critical factor in patient outcomes [32, 33].

Changing Patterns in Thyroid Surgery

As data continue to emerge that reinforce the association between surgeon volume and improved patient outcomes, attention has turned to the effect of these data on referral patterns for patients with surgical endocrine disease. Boudourakis et al. utilized data from HCUP–NIS in 1999 and 2005 to measure if procedures performed by high-volume surgeons changed over time for patients undergoing five oncologic procedures (colorectal surgery, esophagectomy, gastrectomy, pancreatectomy, and thyroidectomy) and two vascular procedures (coronary bypass graft surgery and carotid endarterectomy) [11]. The proportion of patients undergoing thyroidectomy by high-volume surgeons increased from 22.4 % in 1999 to 25.2 % in 2005, an increase of 12.5 %; this correlated with a decrease in the volume of thyroidectomy by low-volume surgeons, from 58.9 to 45.2 % (−23.3 %) [11]. Sosa et al. demonstrated that in patients undergoing thyroidectomy, patients of all racial groups are increasingly being referred to higher-volume surgeons [16]. However, the discrepancy in access to high-volume surgeons remains; between 1999–2000 and 2003–2004, the percentage of white patients who had thyroidectomy by the highest-volume surgeons increased from 1 to 7 % (slope +5.7). In contrast, blacks undergoing surgery by the same group of surgeons increased only from 0.2 to 1.8 % (slope +1.6) during the same time period, and the increase for Hispanics was even more muted (0–1.3 %; slope +1.3) (Fig. 5.2) [16].

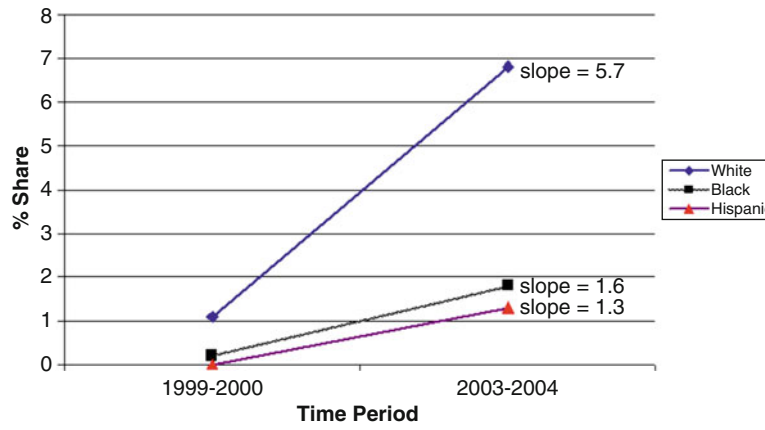

Fig. 5.2 Highest-volume (>100 cases) surgeon share of thyroid procedures, by race over time. Reprinted with permission from Sosa et al. Racial disparities in clinical and economic outcomes from thyroidectomy. Ann Surg 2007; 246: 1083–1091

Surgeon Volume and Extent of Thyroid Surgery

The extent of thyroid surgery performed (thyroid lobectomy vs. total thyroidectomy) is dependent on the indications for surgery. Particularly for patients with differentiated thyroid cancer, there remains controversy as to the appropriate extent of thyroidectomy, with the risks of complications (recurrent laryngeal nerve injury and/or hypoparathyroidism) juxtaposed to the risk of recurrent disease [37–39]. A recent study by Hauch et al. utilized NIS data from 2003 to 2009 to compare the risk of complications between thyroid lobectomy and total thyroidectomy and the effect of surgeon experience on outcomes [40]. Surgeon volume was categorized as low (<10 thyroidectomies per year), intermediate (10–99), or high (>99), for a total of 62,722 cases. Overall, postoperative complications occurred in 10,257 (16 %) of cases. When evaluating the risk of complication by the extent of surgery, the majority of complications were seen to occur after total thyroidectomy (72 %) compared to thyroid lobectomy (28 %; $p<0.0001$). On multivariate analysis, this association persisted, with total thyroidectomy more likely to result in a complication than thyroid lobectomy (odds ratio [OR] 2.15, 95 % confidence interval [CI] 1.99–2.33; $p<0.0001$), and this was a robust finding irrespective of surgeon volume. On adjusted analyses, there was a higher risk of complications after total thyroidectomy for both low-volume (OR 2.37, 95 % CI 2.14–2.62; $p<0.0001$) and high-volume surgeons (OR 1.82, 95 % CI 1.46–2.28; $p<0.0001$) [41]. These data suggest that total thyroidectomy is not without an increased risk of postoperative morbidity, even in the hands of experienced surgeons, and that the decision to perform thyroid lobectomy vs. total thyroidectomy requires careful discussion by surgeon, endocrinologist, and patient.

Conclusion

In summary, recent population-based studies have demonstrated that for patients undergoing thyroidectomy, outcomes are improved when thyroidectomy is performed by a high-volume surgeon, irrespective of surgeon specialty. This is particularly true for vulnerable populations, including the elderly, children, and patients of a racial/ethnic minority. Despite trends that demonstrate increasing referrals to high-volume surgeons, disparities in access remain a challenge for policymakers, payers, and the public at large. Part of the solution well might pertain to the need to increase the supply of high-volume surgeons, especially given the observed increase in both the number of thyroid nodules identified on radiographic studies and the number of thyroid fine needle aspirations performed in the United States,

which almost certainly has in part explained the observed increase of 31 % in the number of thyroid nodule-related surgeries being performed at the national level [41, 42]. There has been a simultaneous increase in the incidence of thyroid cancer in the United States, up to more than 150 % over the last decade.

In addition, access to high-volume providers is almost certainly compromised by disparities in the geographic distribution of the most expert surgeons. For example, data have demonstrated that there is a relative scarcity of high-volume thyroid surgeons in certain geographic regions of the United States, and this might be associated with at least some of the observed disparities seen among under-represented minorities [25]. In the end, the increase in diagnostic testing and surveillance imaging and evolving epidemiology of thyroid cancer will likely result in expanded need for thyroid surgeons in order to optimize quality of care and patient outcomes. The challenge will be for educators to think together with policymakers and payers to assure that there is adequate and distributed supply to meet that demand. Going forward, practice guidelines well might include data related to provider volume when formulating best practice recommendations in the arena of thyroid disease.

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Ambulatory Thyroid Surgery: Is This the Way of the Future?

6

Samuel K. Snyder

Introduction

Outpatient thyroidectomy has been demonstrated in recent years as safe and feasible by a number of endocrine surgery centers (Table 6.1) [1–14]. However, despite the inherent benefits of doing surgery with the same day discharge, the acceptance of thyroidectomy as an outpatient procedure has been slow and still regarded by some as controversial [15, 16]. The American Thyroid Association has recently released a statement on outpatient thyroidectomy that serves as an excellent reference for evaluating the logistics as well as the pros and cons of doing thyroidectomy with the same day discharge [17]. This manuscript addresses the same issues from the perspective of the author's approximate 20-year experience with outpatient thyroidectomy.

Pros and Cons of Outpatient Thyroidectomy

It is important to understand that for most surgeons who perform endocrine surgery, the accomplishment of thyroidectomy in the outpatient setting is a gradual and evolutionary process. It starts with the least risky procedures, parathyroidectomy and/or partial thyroidectomy, and then evolves to include thyroid lobectomy, then total thyroidectomy for a diverse array of pathologies, and finally total thyroidectomy with central lymph node dissection. The safety of the procedure to the patient is paramount and rests primarily in avoiding the risk of life-threatening postoperative bleeding. Each surgeon must evaluate their personal experience with thyroidectomy to assess whether in their hands, it can be done safely in the outpatient setting. Outpatient thyroidectomy is not for every patient, but in the author's experience, with careful patient selection, it can be accomplished for between 80 and 90 % of procedures [8]. It is appropriate to examine the advantages and disadvantages of outpatient thyroidectomy from the perspectives of the patient, hospital, surgeon, insurance company, and society.

Patient There are advantages of being in the comfort of a familiar home environment with family or a caring friend. Even a hotel room can provide a quiet environment with fewer

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interruptions, a comfortable bed, and personal food choices. It can even be less costly if the patient must pay a remaining percentage of insurance charges and/or required co-payments. Finally, being outside the hospital environment can avoid rare hospital acquired infection risks, medication errors, or service and medication delays from caregivers. The disadvantages include losing the presumed safety net of the hospital environment with prompt attention for emergency care. Access to emergency evaluation may be compromised or delayed outside of the hospital. The fear of this unknown problem prompts some patients and their family or friends to be wary of outpatient surgery. In the author's experience, however, the vast majority of patients are relieved and very receptive to having their surgery as an outpatient procedure.

Hospital Outpatient surgery opens up hospital beds to utilization for the care of sicker patients, ultimately reducing the overall physical plant needs, staffing, and overhead costs. The hospital, however, may lose potential reimbursable charges.

Surgeon The benefits of outpatient surgery accrue primarily with the more efficient use of time by eliminating hospital rounding, charting, etc. The surgeon, however, may lose the comfort of knowing that any problems with the patient's recovery are being readily addressed within the hospital environment.

Insurance Company Outpatient surgery saves expenditures. Government restrictions, reasonable or not, can sometimes mandate inpatient care.

Society The penultimate global concern is how to reduce the burden of health-care expenditures while still providing quality health care. Outpatient surgery clearly saves health-care dollars.

Developing an Outpatient Thyroidectomy Program

Outpatient thyroidectomy is not universally applicable to all patients. The surgeon must determine if patient comorbidities require in-hospital postoperative care. The surgeon must also determine if the difficulty and extent of the thyroidectomy procedure increases the risk of postoperative complications that are best addressed in the hospital environment. Social concerns for adequate family support and travel restrictions may limit the feasibility of outpatient surgery. The hospital or outpatient surgery center must have a system designed to promote outpatient surgery with adequate patient evaluation and counseling prior to discharge. In the author's main hospital, the same day discharge center will stay open to midnight to facilitate outpatient surgery.

The experience with laparoscopic cholecystectomy as an outpatient procedure in the last decade of the twentieth century is analogous to doing outpatient thyroidectomy currently. Historically, open cholecystectomy required a hospital stay for a few days before discharge. There were financial pressures to increasingly shorten the hospital stay. Then laparoscopic cholecystectomy was developed, which made the recovery less painful. It became apparent that the surgery could be tolerated as an outpatient procedure for most patients. The risk of postoperative bile leak, bleeding, or other serious complications was very rare, but not to be overlooked. Eventually, the standard of care favored outpatient laparoscopic cholecystectomy. A culture of expectation of outpatient surgery for this procedure by patients and health-care providers developed, such that patients are now dismissed from the same day surgery center as soon as they meet discharge criteria, usually within a few hours.

The evolution of outpatient thyroidectomy has been much slower than it was for laparoscopic cholecystectomy. This has occurred despite the awareness that most patients tolerate thyroidectomy as well as laparoscopic cholecystectomy from a discomfort point of view. Serious life-threatening complications are similarly rare, but

Table 6.1 Outpatient thyroidectomy outcomes

Study	Year	Outpatient thy (#)	% of all thy	% total thy[a]	Observation (h)	% hematoma	Fatal hematoma	% hypocalcemia	% readmit
Snyder	2006	51	88	24	3.3	2.0	0	5.2	3.9
Spanknebel	2006	778	65	59	≥6	–	0	–	–
Terris	2007	52	57	33	–	1.9	0	0.0	1.9
Inabnet	2008	180	80	43	≥5	0.4	0	1.3	–
Champault	2009	77	50	0	≥6	0	0	0	0
Trottier	2009	234	99	26	≥4	0.4	0	2.6	1.7
Seybt	2010	208	50	38	–	0.5	0	1.9	1.9
Snyder	2010	1064	86	58	2.7	0.2	0	5.2	1.6
Hessman	2011	138	77	46	–	1.4	0	3.6	2.9
Houlton	2011	95	53	100	–	0	0	0	0
Sklar	2011	94	38	0	≥4	0	0	0	0
Tuggle	2011	1168	17	33	–	–	0	–	1.4
Mazeh	2012	298	49	29	3–4	0	0	1.7	0
Sahmkow	2012	176	88	47	≥3	0	0	10.0	1.7

All studies et al.; thy = thyroidectomy; observation (h) = observation period following surgery in hours; hematoma = postoperative cervical hematoma; hypocalcemia = postoperative symptomatic hypocalcemia; readmit = postoperative hospital admission for thyroidectomy-related complications following outpatient thyroidectomy

[a]Total thyroidectomy includes completion thyroidectomy procedures (Reprinted with permission of Thyroid 23:1193–1202, 2013)

again not to be overlooked. The author's personal evolution toward doing outpatient thyroidectomy began in the last decade of the twentieth century with the experience of using local anesthesia with intravenous sedation for parathyroidectomy that allowed the patient to be dismissed the same day. Some patients had a dominant thyroid nodule that needed to be addressed at the same time as the parathyroidectomy. It was impressive how well they tolerated the additional partial thyroidectomy under local anesthesia. The experience of Dr. LoGerfo with thyroidectomy under local anesthesia with intravenous sedation [18] led the author to further utilize this approach with thyroid lobectomy, total thyroidectomy, and eventually total thyroidectomy with a central level VI lymph node dissection. The main advantage of local anesthesia surgery is the rapid postoperative recovery, which makes discharge of the patient the same day more feasible, much like the same day thyroidectomy discharge as promoted by Dr. LoGerfo [18]. A randomized prospective comparison of thyroidectomy under local anesthesia with intravenous sedation versus general anesthesia was conducted, and both groups were planned for outpatient thyroidectomy to see if there was an advantage to the local anesthesia approach. Patient satisfaction and results were surprisingly nearly identical. Complications occurred but could still be managed safely when they developed [1]. This led to the increasing utilization of outpatient thyroidectomy until approximately 80–90 % of thyroidectomies presently are done as outpatient procedures [8]. The author's outpatient surgery center and main hospital center are geared toward providing the immediate postoperative support that allows the patient to be discharged home the same day. With this creation of a culture of outpatient thyroidectomy, the patient response to proposed outpatient surgery is universally positive. There is occasional push back from the patient and family for social and healthcare concerns, but it is rare to have a patient be adamant about being hospitalized after surgery.

So why is there so much resistance by surgeons for doing outpatient thyroidectomy when the feasibility seems so evident? The answer rests in the overriding concern for postoperative hemorrhage in the central neck resulting in airway compromise from a life-threatening hematoma. Other major complications include symptomatic hypocalcemia from hypoparathyroidism and recurrent laryngeal nerve injury. A secondary overriding concern relates to problems with timely access to qualified emergency care, if needed. It is relevant to address each of these concerns in depth.

Postoperative Central Neck Hematoma: Incidence and Timing

Despite intensive efforts by the surgeon to avoid postoperative central neck hematoma, this complication predictably will occur in a very small percentage of patients. A number of studies have evaluated the incidence and timing of postoperative hematoma to formulate recommendations on the feasibility and safety of doing outpatient thyroidectomy (Table 6.2) [19–32]. The frequency of postoperative hematoma is approximately 1 % or less. Patient factors that increase the risk of postoperative bleeding have not been clearly defined although the author found a tendency toward increased bleeding risk in patients on anticoagulants [32]. It is important to keep in mind that most studies that report on postoperative central neck hematoma include all thyroidectomy procedures. Since outpatient thyroidectomy is done for selected patients deemed by the surgeon to have a lower risk for postoperative bleeding, the incidence of this complication then should be less. The author reported on all thyroidectomy procedures over a 6-year period of time during which postoperative bleeding occurred in 0.19 % (2/1064) outpatient thyroidectomies and 1.4 % (3/208) inpatient thyroidectomies [8]. The timing of postoperative bleeding varies among reported case series (Table 6.2). In general, about half will occur within 6 h of the surgery, a third within 7–23 h of the surgery, and the remaining 24 h or more after surgery. The author with coauthors Dixon, Lairmore, and Govednik reported on an institutional 17-year experience with postoperative hematoma following thyroidectomy and/or parathyroidectomy

procedures and noted an incidence of 0.51 % (17/3357) after thyroidectomy; 38.9 % of bleeding overall occurred within 6 h after the surgery, 38.9 % between 7 and 23 h after the surgery, and 22.2 % from 24 to 96 h after the surgery [32]. Only two patients needed emergency bedside decompression of the cervical hematoma as a life-saving effort, and both occurred in the postoperative anesthesia care unit (PACU) within 2 h of the surgery. The remaining hematomas were surgically managed in the operating room. Half of the hematomas occurred in patients that had outpatient thyroidectomy. It is noteworthy that a predictable percentage of hematomas occur after 23 h following surgery. There are a number of studies that advocate a 23-h observation period following surgery as the optimal observation period before safely discharging the patients [15, 16, 33]. Yet this policy will still miss a defined percentage of postoperative bleeding episodes. A purist assessment would advocate a 2–4-day postoperative hospitalization to have every bleeding episode occur within the hospital environment. If outpatient thyroidectomy is contemplated, how long should the patient be observed in the day surgery unit prior to discharge? This is a judgment decision by the surgeon and relates to the perceived risk of postoperative bleeding. Six hours has been used by some surgeons [2, 5]. The author with coauthor's reported experience on postoperative hematoma indicated that only bleeding occurring in the PACU needed emergency bedside decompression as a life-saving effort [32]. Therefore, in the author's experience, patients deemed appropriate for outpatient thyroidectomy are dismissed from the day surgery unit when they meet the usual dismissal criteria plus observational evidence of no deep cervical wound bleeding. Trained nursing staff should be able to make that determination with surgeon input only as deemed necessary. Essentially, dismissal criteria are not much different from what would be used for a laparoscopic cholecystectomy with the exception of the assessment of the cervical wound. The author reported an average postoperative observation period of 2 h and 42 min prior to dismissal from the day surgery unit [8].

The relative risk of postoperative hematoma for an individual patient should be less for unilateral thyroidectomy than bilateral thyroidectomy, since the latter surgery requires hemostasis of almost twice as many blood vessels. Reported results seem to bear this out. A large Austrian study reported a significantly higher risk of postoperative hematoma for total thyroidectomy versus thyroid lobectomy (2.0 % vs. 1.0 %, $p < 0.001$) [31]. The author's experience also demonstrated a 0.62 % occurrence of postoperative central neck hematoma after bilateral thyroidectomy procedures with or without parathyroidectomy versus a 0.38 % occurrence following unilateral thyroidectomy procedures with or without parathyroidectomy [32]. This has led some surgeons to be more willing to do outpatient thyroidectomy for thyroid lobectomy than total thyroidectomy [34]. The increased risk of postoperative cervical hematoma after total thyroidectomy appears to be just related to the more extensive surgery. There is no reported evidence that a cervical hematoma after total thyroidectomy is more life-threatening than a cervical hematoma after thyroid lobectomy. A central lymph node dissection plus total thyroidectomy should add minimal extra risk to the development of a postoperative cervical hematoma. The additional risk is mainly from thymic veins and small segmental tracheal arteries that need additional hemostasis.

Postoperative Central Neck Hematoma: Prevention

Complete hemostasis to prevent post-thyroidectomy central neck hematoma is the obvious solution to accomplishing outpatient thyroidectomy safely. Some technical considerations to achieve hemostasis deserve emphasis. Traditionally, the patient was placed in the slightly head-up or "beach chair" position to reduce venous pressure and therefore reduce intraoperative venous bleeding. However, this may obscure venous bleeding sites. The amount of blood loss during thyroidectomy is rarely substantial enough to have hemodynamic consequences. The author prefers the supine position

Table 6.2 Thyroid postoperative hematoma

Study	Year	Thy (#)	% bilateral thy	% hematoma	Fatal hematoma	% <6 h	% 6–24 h	% >4 h
Shaha	1994	600	42	1.3	0	100	0	0
Bergamaschi	1998	1192	67	0.8[a]	1	~60	~10	~30
Reeve	2000	10,201	–	1.2	0	–	–	–
Burkey	2001	7921	–	0.3	0	43[b]	37[b]	19[b]
Zambudio	2004	301	100	1.0	0	–	–	–
Materazzi	2007	1571	71	0.6[a]	0	~70	30 (<10 h)	0
Bergenfelz	2008	3660	45	2.1	0	–	–	–
Leyre	2008	6830	74	1.0	0	53	37	10
Rosenbaum	2008	838	55	0.7	0	67 (<4 h)	16.5	16.5
Bononi	2010	562	–	0.5	0	0	67	33
Chang	2010	1935	100	1.0	0	–	–	–
Lang	2012	3086	68	0.7[a]	0	73	27	0
Promberger	2012	30,142	–	1.7	3	81	17	2
Dixon	2014	3357	53	0.5	0	39	39	22

All studies et al.; *thy* = thyroidectomy; hematoma = cervical hematoma

[a]Excludes hematomas not operated on but observed: Bergamaschi et al. 9 hematomas, Materazzi et al. 5 hematomas, and Lang et al. 19 hematomas

[b]Percentages are for the total study of 7921 thyroidectomies (21 hematomas) + 5896 parathyroidectomies (21 hematomas) (Reprinted with permission of Thyroid 23:1193–1202, 2013 with added data)

for thyroidectomy to allow venous bleeding sites to be more readily identified for hemostasis during the operation. Traditionally, subplatysmal flaps are advocated by thyroid surgeons to augment the exposure of the thyroid gland. This requires dissection along the anterior jugular veins, which can place the subcutaneous wound at increased risk of postoperative venous bleeding with Valsalva maneuvers. Thyroidectomy can be accomplished readily without active subplatysmal flap dissection just by maximizing the midline exposure, which is the author's preference. The frequently present midline anterior jugular veins can be ligated at wound opening or closure as indicated.

During thyroidectomy, there are a multitude of vessels that require hemostasis to prevent postoperative hematoma, many of which are not detailed in anatomy textbooks. The major venous channels are the isthmus, middle thyroid, superior thyroid, and thymic veins. As lower pressure blood vessels, they less often contribute to postoperative hematoma. The arterial blood vessels deserve more attention intraoperatively. In addition to the inferior thyroid, superior thyroid, and infrequent thyroid ima arteries, substantial arterial vessels are frequently located at the medial border of the cricothyroid muscle, the junction of the cricoid cartilage, and the trachea that the author likes to refer to as the "thyroid uma arteries," ligament of Berry area, and segmental tracheal arterioles (Fig. 6.1a). The author has witnessed a resulting postoperative hematoma from each of these sites. All of these potential arterial bleeding sites become more evident in patients with Graves' disease. The use of loupe magnification during thyroidectomy enhances the visualization of potential bleeding sites, particularly small vessel side branches that may be in spasm during wound exploration but at risk of initiating postoperative bleeding (Fig. 6.1b). Careful inspection of the entire wound for these enumerated major bleeding sites following completion of the thyroidectomy is paramount to avoiding postoperative bleeding. The author likes to place additional small ligaclips on these at-risk bleeding sites, particularly in the ligament of Berry area and "thyroid ima arteries" prior to

completing wound closure. It is helpful to do the larger, more vascular, and more difficult thyroid lobe first when planning a total thyroidectomy to allow for a greater lapse of time to ensure adequate hemostasis prior to wound closure. The presence of a small hematoma on the first thyroid lobectomy side indicates the location of a residual bleeding site that needs further hemostasis. Other measures to assist in identifying potential residual bleeding sites following completion of the thyroidectomy include an induced Valsalva maneuver by anesthesia to raise venous pressure, wound dabbing, and/or gentle rubbing combined with irrigation.

Hemostasis can be effectively accomplished with vessel suture ligation, vessel clips, electrocautery, or other high-energy devices. The author uses all of these methods but prefers mechanical hemostasis of major blood vessels. A significant difference in effective hemostasis has not been demonstrated between these hemostatic methods [35, 36]. The recently published large study from Austria indicated a small rise in the incidence of postoperative hematoma after thyroidectomy in recent years (1979–1983 1.0 %, 1989–1998 1.7 %, 2004–2008 2.4 %), but the cause of this is open to speculation [31]. It is unclear whether hemostatic techniques played a significant role in this observation. Perhaps a more telling result was the demonstration by the Austrian study of significant differences in the rate of postoperative hematoma among surgeons (0.4–2.8 %, $p < 0.001$) [31]. Individual surgeons contemplating doing outpatient thyroidectomy need to demonstrate a correspondingly very low postoperative hematoma rate, if any. A variety of hemostatic pads or clotting aids are commercially available to apply to the thyroidectomy bed to augment principally small vessel hemostasis before wound closure. There is unlikely to be any statistical evidence to support this endeavor, but the practice of adding hemostatic agents to the thyroidectomy bed seems reasonable.

A wound closure method for the strap muscles that is minimal with a single figure-of-eight suture or by leaving the lower portion of the strap muscles open has been proposed to enhance earlier recognition of significant deeper postoperative bleeding as the blood diffuses into the subcutaneous spaces [3, 18]. The use of drains left in the thyroidectomy bed to also enhance earlier recognition of postoperative bleeding has not been proven to be useful [17]. These have the theoretical potential to disturb hemostasis at the time of drain removal. The author does not use drains. Coughing and straining are to be avoided during extubation at the end of the operation [37]. Deep extubation by anesthesia, if reasonable, can accomplish this. Avoiding nausea and vomiting in the early postoperative recovery is also desirable. A number of pharmacological agents given during and after the operation can assist in this. A final practical measure to facilitating outpatient discharge is to anesthetize the wound with a long-acting local anesthetic, which may help minimize the early need for narcotic pain medication and thus side effects associated with pain medication.

Postoperative Central Neck Hematoma: Management

It is important to keep in mind the evolution of neck wound dressings over time. Historically, patients having thyroidectomy decades ago had bulky dressings, e.g., Queen Anne's dressing, to apply a modicum of pressure to the wound to limit postoperative bleeding. At the author's institution in 1980, it was a standard practice for older surgeons to use this kind of dressing while placing every thyroidectomy patient in the intensive care unit with a tracheostomy set at the bedside for fear of a postoperative hematoma. However, the anterior neck is not an area that can be adequately compressed to contribute to hemostasis. The bulky dressings merely hid a developing hematoma until the patient was extremely symptomatic, potentially contributing to the morbidity of this complication. Older studies on the incidence, timing, and severity of postoperative hematoma likely included patients managed with bulky dressings. Today, the optimal wound coverage is a minimal gauze dressing barely covering the wound or perhaps no dressing with a plastic sealant dressing. This gives ready visual

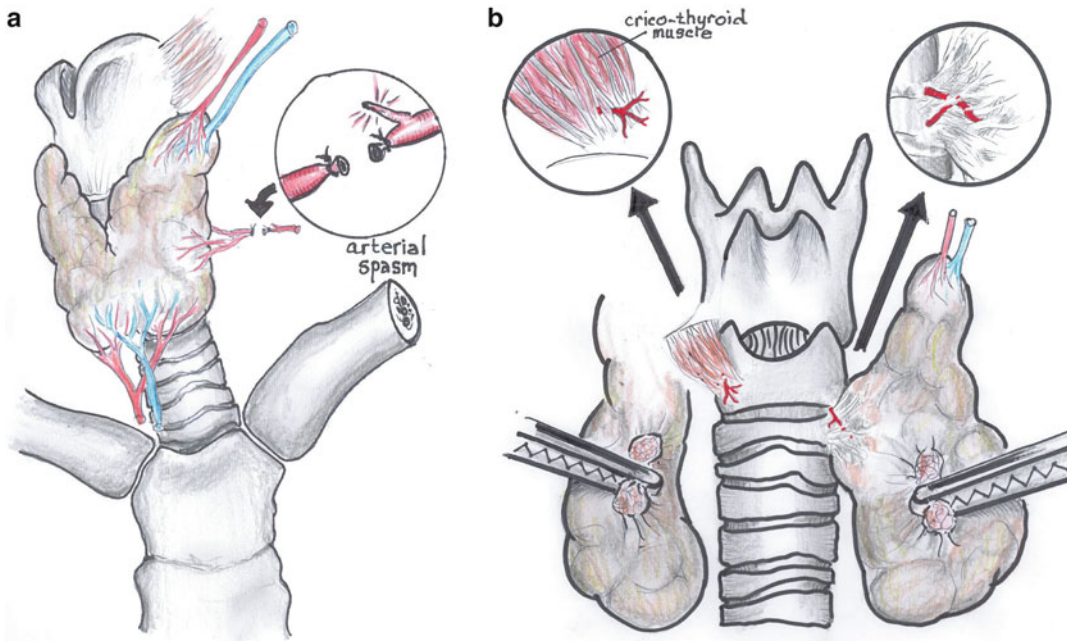

Fig. 6.1 (**a** and **b**) Frequent missed sites of bleeding with thyroidectomy (Reprinted with permission from World J Surg 38(6):1262–1267, 2014)

access to the anterior neck to detect a developing hematoma, sometimes even before it becomes symptomatic.

Postoperative central neck hematoma can be a lethal complication. A rapidly expanding hematoma from major arterial bleeding can produce significant tracheal pressure to compromise the airway. This is verified by decreasing oxygen saturation and the patient's waning ventilatory status. The classic management of this clinical situation is bedside decompression by promptly opening the wound, removing closing sutures, evacuating the hematoma, and even performing a tracheostomy in extremis conditions to reestablish an airway. Attempts at endotracheal intubation in this clinical situation are fraught with difficulty and serve only to delay proper life-saving treatment. Most reported studies do not indicate how often bedside decompression was necessary or the mortality of postoperative hematoma. In the author's experience, bedside decompression of a hematoma is rarely necessary and primarily limited to a rapidly enlarging hematoma that becomes evident shortly after surgery is completed while the patient is in the postoperative anesthesia care unit (PACU) [32].

The more common clinical scenario is a slowly expanding central neck hematoma from small arteriole or venous bleeding that produces a mild- to moderate-size hematoma. The gradually increasing central neck compartment pressure leads to laryngeal edema that can contribute to compromising the airway. The patient complains of progressive neck swelling and/or tightness. The patient has difficulty putting the chin down on the chest without experiencing increased tightness or a choking sensation. As the swelling increases, the patient has difficulty lying flat, because of increased shortness of breath. The patient prefers sitting upright with the neck slightly extended, which maximizes the airway opening. With increasing laryngeal edema, the patient may develop stridorous breathing. The diagnosis of postoperative central neck hematoma is generally a clinical one. Ultrasound of the central neck is difficult to interpret secondary to postoperative swelling and the interference from hemostatic pads that may have been placed at the time of wound closure. Computerized

tomography scan of the neck can be helpful to establish the diagnosis, but usually it delays proper treatment, which is wound decompression. Attempts at endotracheal intubation are again fraught with danger, because of the risk of inducing laryngeal spasm and life-threatening airway compromise.

The initial management of the patient with a central neck hematoma requires confirming adequate oxygenation with O_2 saturation measurements, with or without supplemental oxygen. Keeping the patient in the upright position promotes this. The patient needs urgent central neck decompression. The author prefers to accomplish this in the controlled environment of the operating room. Anesthesia and the operating room staff are aware of the emergency nature of this intervention. Surgical staff accompanies the patient to the operating room, maintaining the upright position. The patient is prepped awake in 45° upright position. Using local anesthesia, the cervical wound is opened and hematoma evacuated. The patient can now tolerate the supine position without respiratory difficulty. Continuing under local anesthesia with some mild sedation, the wound can be searched for the bleeding source. Irrigation of the wound with a dilute hydrogen peroxide solution helps clear residual blood clot. Hemostasis is established with ligation of the bleeding site or confirmed by excluding a persistent active bleeding site, which is frequently the end result of wound exploration. If successful, the operation can be completed safely under local anesthesia with mild sedation. If general anesthesia is felt necessary to facilitate an adequate wound exploration for hemostasis, the patient can be intubated once they can tolerate the supine position. It is reasonable for the anesthesia team to consider pursuing awake intubation with endoscopic guidance as the safest approach in this situation, because of the anticipated laryngeal edema that makes securing the airway more difficult. The irritated larynx appears to be more susceptible to develop laryngeal spasm with endotracheal intubation attempts. If the patient has been paralyzed already with succinylcholine, an emergency surgical airway with tracheostomy is needed. The author has experienced just this set of circumstances on one occasion. Tracheostomy is readily accomplished, however, with the wound already opened and trachea exposed. If concern about maintaining an adequate airway remains following completion of the wound exploration, the patient can be left intubated for a period of time, maintained in a semi-upright position, and given steroids to reduce laryngeal edema before extubation can later be safely accomplished. This sequence of events for management of the central neck hematoma can be accomplished similarly for the hospitalized patient or for the outpatient from the emergency room. Again, in the author's experience, the vast majority of patients with central neck hematoma can be managed without initial bedside decompression of the cervical wound [32].

Postoperative Hypoparathyroidism

The development of symptomatic hypocalcemia secondary to hypoparathyroidism is not really an impediment to successful outpatient thyroidectomy. It is a risk factor only after total thyroidectomy or completion total thyroidectomy. The nadir of postoperative hypocalcemia is typically 48–72 h postoperatively when symptoms become more evident. The short half-life of parathyroid hormone in the blood allows measuring PTH in the day surgery unit or PACU to select patients for oral supplemental calcium plus calcitriol [38]. Various time frames from immediately after surgery to 6 h postoperatively have been reported to correctly predict significant hypocalcemia [39]. Generally, an intact parathyroid hormone level below 10–15 is used to prescribe postoperative calcium medication [40]. The alternative approach is to recommend routine oral calcium supplementation postoperatively for total thyroidectomy [41]. The medication is inexpensive and highly unlikely to result in significant hypercalcemia. It is helpful to keep in mind that there are differences among calcium medications as to the elemental calcium content, which is 40 % for the more commonly used calcium carbonate. Oscal brand does specify a level of 500 mg of

elemental calcium with each tablet. Calcium citrate preparations are more readily absorbed in patients with altered gastrointestinal function, i.e., Roux-en-y gastric bypass. Calcitriol can be added at the surgeon's discretion, if there is increased concern for less than ideal blood supply to parathyroid glands intraoperatively or very low postoperative parathyroid hormone levels (<10). The need for autotransplantation of only one parathyroid gland has not been shown to increase the risk of early postoperative symptomatic hypocalcemia [42]. If symptomatic hypocalcemia does develop despite supplemental oral calcium, it can frequently be successfully managed in the outpatient setting with only a very small percentage of patients needing in-hospital treatment [8].

Recurrent Laryngeal Nerve Injury

Bilateral recurrent laryngeal nerve injury is a contraindication to outpatient thyroidectomy and should be immediately evident following extubation in the operating room or PACU. Unilateral recurrent laryngeal nerve injury is not a contraindication to outpatient thyroidectomy [8]. Patients, however, are at increased risk for aspiration, particularly with oral liquids. This leads to frequent coughing that can then foment postoperative internal bleeding in the central neck compartment. Patients can reduce the risk of aspiration by taking oral liquids in small amounts (drinking through a straw) and tilting the head down and to the side of the injury to mechanically protect the airway during swallowing.

The patient's voice quality is a poor diagnostic aid to identify unilateral recurrent laryngeal nerve injury in the immediate postoperative period. Intraoperative recurrent laryngeal nerve monitoring, particularly using electrode-bearing endotracheal tubes with an electromyographic monitor, can indicate the presence of a recurrent laryngeal nerve injury [43]. If a total thyroidectomy is planned and the first lobectomy side indicates a recurrent laryngeal nerve that is anticipated to recover within the next few months, then a completion total thyroidectomy with contralateral lobectomy is delayed until adequate vocal cord function returns on the initial affected side [44]. This avoids the risk of bilateral recurrent laryngeal nerve injury and still allows the thyroidectomy surgery to be done as an outpatient procedure. When intraoperative nerve monitoring indicates the presence of a recurrent laryngeal nerve injury, the surgeon can now counsel the patient about the altered voice function that is anticipated and the proper maneuvers to avoid aspiration of liquids with swallowing [44]. This knowledge allows safe discharge of the patient from the day surgery unit and avoids increased risk of postoperative bleeding associated with aspiration-induced coughing.

Outpatient Thyroidectomy: Social Concerns

A program of outpatient thyroidectomy requires detailed oral and written instructions about potential postoperative complications, particularly the signs and symptoms of bleeding into the thyroidectomy bed, the response to these complications in seeking emergency evaluation when indicated, where to seek emergency evaluation, and contact information during the day or night for advice concerning possible complications. All of these instructions can be covered before and once again after the surgery. The patient needs involved family or friends that appear to understand instructions about potential complications and are readily able to provide assistance, especially in the early postoperative period.

Adequate transportation to an emergency facility is a necessary consideration for outpatient thyroidectomy. Ideally, this would be to the institution where the surgery took place. If travel from home would be considered too distant or too difficult from the hospital to be safe, then the patient, family, and/or friends are counseled to stay in a nearby hotel or motel for at least the first postoperative night. How far is too far is a judgment decision between the surgeon and patient, family, and/or friends. The author's experience with patients that have had a postoperative cervical hematoma following outpatient thyroidectomy

has not identified a prohibitive distance from the hospital. Intuitively, a separation of greater than 1–2 h would be considered problematic. All these social concerns, if not adequately resolved, could contraindicate proceeding with outpatient thyroidectomy.

Patient Selection

So which thyroid operations and which pathologies should or should not be done as outpatient procedures? There are no absolute contraindications, meaning even a multinodular goiter with substernal extension, Graves' disease, or thyroid cancer can be considered a candidate for outpatient thyroidectomy. Patients needing a lateral cervical lymph node neck dissection, however, are excluded from this consideration. It is a judgment decision by the surgeon concerning the extent of the operative procedure, relative risk of postoperative bleeding, patient comorbidities, adequate initial postoperative observation in the day surgery unit, and adequate supportive outpatient social circumstances. It is not related to how much blood loss occurred during the operation, but how thorough and complete hemostasis appears at the end of the operation. While the surgeon cannot universally predict who will develop postoperative bleeding, the relative risk can be assessed, so that patients felt to be at significantly increased risk can be observed in the hospital setting. The author reported an incidence of postoperative cervical hematoma of 0.19 % for outpatient procedures and 1.4 % for inpatient procedures that indicates prudent patient selection [8].

Conclusion

With all these considerations in mind, outpatient thyroidectomy is feasible and safe for the majority of thyroid operations while providing similar health-care cost savings to society as other outpatient operations. It seems reasonable to anticipate increasing utilization of outpatient thyroidectomy by experienced thyroid surgeons in the future. A recent study confirms that this is already taking place at major university hospitals [45]. Ultimately, the majority of thyroidectomy procedures will be accomplished in the outpatient setting to the benefit of the patient, hospital, surgeon, insurance company, and society.

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Robotic Thyroidectomy: Is There Still a Role?

7

William S. Duke and David J. Terris

Rationale for Remote Access Thyroid Surgery

Thyroid surgery, which had persisted essentially unchanged since the time of Kocher, has experienced an explosion of new developments in the last decade. Advanced energy devices and refinements in postoperative management strategies are improving the safety of the procedure, while minimally invasive concepts and video-assisted techniques have allowed for drainless, outpatient surgery with a faster recovery time and reduced cosmetic impact compared with conventional thyroid surgery. Despite these advances, thyroid surgery through an anterior cervical incision still leaves a scar in a visible location. Regardless of how small or well-camouflaged this scar may be, the prospect of any incision on the visible portion of the neck is an unpalatable proposition for some patients.

In an effort to further reduce the cosmetic impact of thyroid surgery, in the late 1990s surgeons in Asia began to experiment with attempts to completely remove the thyroidectomy scar from the anterior neck [5, 6]. This was driven largely by a tendency toward hypertrophic scarring in this patient population, as well as adverse cultural perceptions toward neck scars. These remote access approaches, which move the incision from the visible portion of the neck to a location concealed from public view, would serve as the foundation for the remote access robotic thyroidectomy procedures employed today.

History of Remote Access Thyroid Surgery

The earliest attempts at remote access thyroid surgery were endoscopic procedures with the incisions placed in the axilla or breast [5, 6]. While these approaches achieved some measure of popularity in Asia, they were not adopted by Western patients or surgeons. In addition to differing attitudes toward cervical and breast scars between these two patient populations [7, 8], there were inherent limitations, particularly a two-dimensional view of the surgical field, long dissection with rigid instruments, and the need for CO_2 insufflation to maintain the operative space. A gasless endoscopic axillary approach emerged [9] which overcame some of these challenges. However, it was the marriage between the robotic surgical platform and this gasless transaxillary remote access approach to the thyroid in 2009, promoted by the Chung group in Seoul, that spawned the modern era of robotic thyroid surgery [10].

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The robotic system offers several key advantages over endoscopic surgery. The high-definition binocular camera system provides a three-dimensional view of the operative field. The robotic instruments articulate in such a way that they can achieve or even surpass the range of motion of the human wrist, allowing for improved maneuverability in limited operative spaces. Finally, the surgical robot faithfully reproduces the surgeon's hand movements in a scaled fashion, allowing for precise dissection around critical structures. These advantages helped fuel a global interest in robotic-assisted thyroid surgery that the endoscopic approaches were never able to stimulate. The surgical robot is currently used in both transaxillary and post-auricular approaches to the thyroid in the United States (Fig. 7.1). It is important to appreciate that

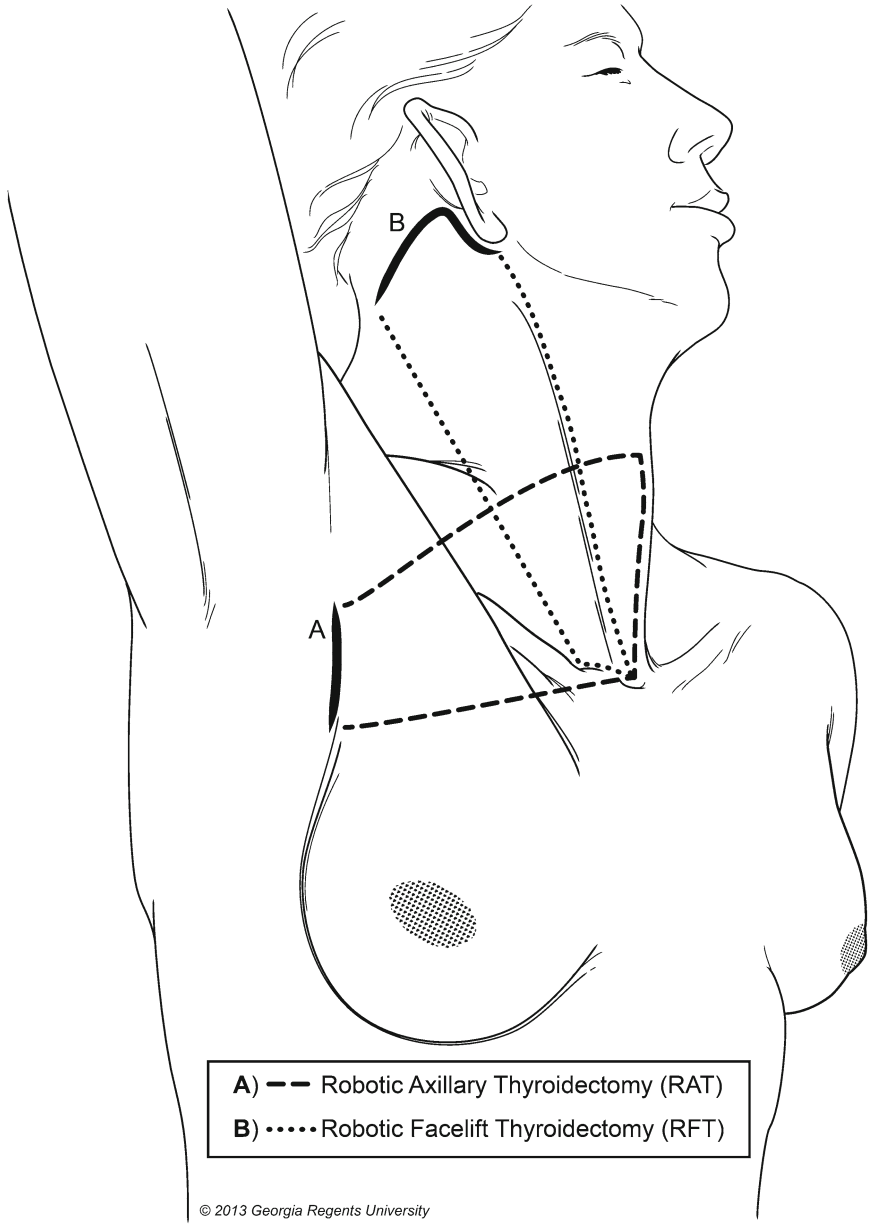

Fig. 7.1 Comparison of the RAT and RFT approaches (from Duke WS, Terris DJ. Alternative approaches to the thyroid gland. *Endocrinol Metab Clin N Am*. 2014;43:459–474, with permission of Elsevier)

"robotic thyroidectomy" is a nonspecific and even misleading term in surgical parlance. The procedure is a remote access thyroidectomy, and the robot is simply a tool used to successfully complete the procedure. Patients should understand that these approaches are not minimally invasive; in all cases they involve more dissection than that associated with the anterior cervical approaches. Patients should also be counseled that these are not "scarless" operations; the scar is simply moved from the visible portion of the neck to a completely hidden, remote location.

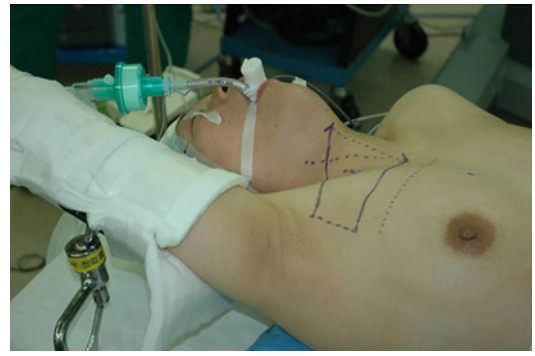

Fig. 7.2 Patient positioning for robotic axillary thyroidectomy (from Ryu HR, Kang SW, Lee SH, et al. Feasibility and safety of a new robotic thyroidectomy through a gasless, transaxillary single-incision approach. *J Am Coll Surg*. 2010;211(3):e13–e19, with permission of Elsevier)

Robotic Transaxillary Thyroidectomy

The remote access robotic-assisted transaxillary thyroidectomy (RAT) was developed to overcome the limitations of endoscopic thyroid surgery. Though no absolute inclusion or exclusion criteria exist for this approach, it is generally indicated for patients with benign or indeterminate nodules ≤5 cm and malignancies ≤2 cm in patients who do not have substernal or extrathyroidal extension of their disease [1, 11, 12]. A unilateral approach is typically performed, though single-incision bilateral procedures have been reported [13, 14], as have large experiences with both central and lateral neck dissections [11, 15].

The procedure has been well described [16, 17] and involves making an incision in the axilla, which is sometimes supplemented with an additional chest incision (Fig. 7.2). A long soft tissue pocket is elevated across the chest, and the thyroid compartment is entered between the sternal and clavicular heads of the sternocleidomastoid muscle. The robot is deployed and the thyroid is removed.

While this procedure offers patients the option of thyroid surgery without a visible neck scar, there are several disadvantages. The operation takes longer to perform than anterior cervical approaches, and the long dissection distance makes stimulation of the recurrent laryngeal nerve (RLN) difficult. In the publications related to this procedure, a drain has always been used and it has been performed on an inpatient basis (although there are some surgeons who reportedly do this without a drain and on an outpatient basis), eliminating many of the advantages achieved by the anterior cervical minimally invasive approaches. Finally, as the procedure was adopted into Western practices, a number of new complications not usually associated with thyroid surgery began to emerge, including brachial plexus neuropathies and visceral organ injuries [1, 3]. For these reasons, this procedure has now been abandoned in most of the Western centers where it was initially implemented [18].

Robotic Bilateral Axillo-Breast Approach Thyroidectomy

The robotic-assisted bilateral axillo-breast approach (BABA) was developed in South Korea to overcome some of the challenges when working in narrow operative spaces using the transaxillary approach [19, 20]. This procedure involves creating bilateral axillary and circumareolar access ports and then elevating soft tissue flaps from the thyroid cartilage to the anterior chest (Fig. 7.3). Unlike the gasless transaxillary approach, BABA utilizes CO_2 insufflation of the neck to maintain the operative space. After creation of the surgical pocket, the robot is docked and the gland removed.

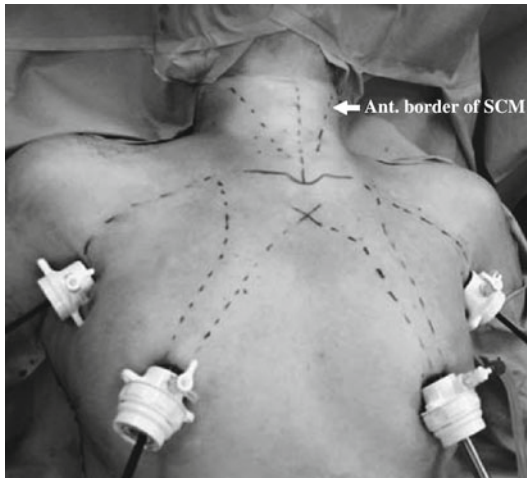

Fig. 7.3 The bilateral axillo-breast approach (BABA), showing axillary and areolar access sites (from Choe JH, Kim SW, Chung KW, et al. Endoscopic thyroidectomy using a new bilateral axillo-breast approach. *World J Surg*. 2007;31:601–606, with permission of Springer)

This two-sided approach has been used to perform bilateral surgery and central neck dissection on patients with a number of thyroid diseases, including Graves' disease, Hashimoto's thyroiditis, and selected thyroid malignancies [20–22], though its use has been limited to South Korean practices, and no reports of BABA in the United States have been published.

Robotic Facelift Thyroidectomy

Despite the problems encountered as RAT was incorporated into Western practices, the concept and potential advantages of robotic-assisted thyroid surgery were recognized as valid and worthy of pursuit. Efforts to create a safer, less morbid remote access robotic approach culminated in the development of the robotic facelift thyroidectomy (RFT) in 2011 [23–25].

Potential candidates for this procedure should have disease that is appropriate for unilateral initial surgery and have no prior history of neck surgery. The dominant nodule should be less than 4 cm, with no concern for substernal or extrathyroidal disease [25].

The RFT procedure begins with an incision in the postauricular crease that is carried into the occipital hairline (Fig. 7.4). A subplatysmal soft tissue flap is elevated, exposing and preserving the great auricular nerve and external jugular vein. The anterior aspect of the sternocleidomastoid muscle is skeletonized inferiorly to the clavicle and the strap muscles are identified (Fig. 7.5). These muscles are retracted ventrally, revealing the thyroid gland. The surgical robot is deployed and the thyroid lobe is removed.

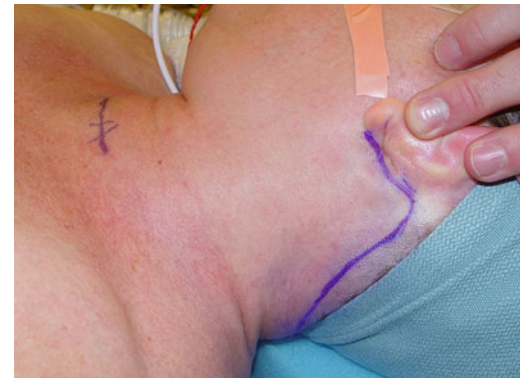

Fig. 7.4 Incision for the robotic facelift thyroidectomy (from Terris D, Singer MC, Seybt MW. Robotic facelift thyroidectomy: patient selection and technical considerations. *Surg Laparosc Endosc Percutan Tech*. 2011;21(4): 237–242, with permission of Wolters Kluwer Health)

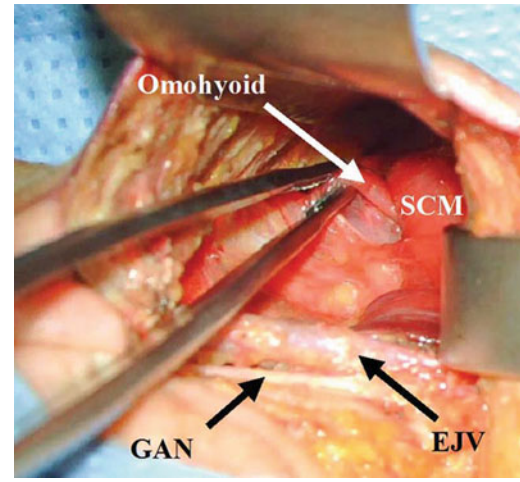

Fig. 7.5 The robotic axillary thyroidectomy dissection pocket, demonstrating the omohyoid muscle and the great auricular nerve (GAN) and external jugular vein (EJV) on the surface of the sternocleidomastoid muscle (SCM) (from Terris DJ, Singer MC, Seybt MW. Robot facelift thyroidectomy: II. Clinical feasibility and safety. *Laryngoscope*. 2011; 121:1636–1641, with permission of John Wiley and Sons)

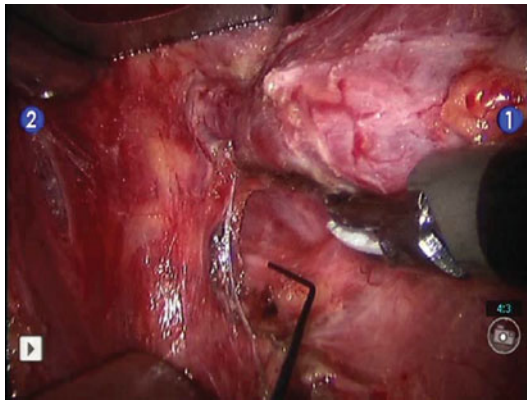

Fig. 7.6 The recurrent laryngeal nerve is easily reached for electrical stimulation during the robotic facelift thyroidectomy (from Terris DJ, Singer MC, Seybt MW. Robot facelift thyroidectomy: II. Clinical feasibility and safety. *Laryngoscope*. 2011;121:1636–1641, with permission of John Wiley and Sons)

Table 7.1 Comparison of remote access robotic-assisted thyroidectomy techniques

Comparison of remote access robotic-assisted thyroidectomy techniques		
Approach	Advantages	Disadvantages
Axillary	No visible incision	Drain required Postoperative inpatient care Risk of brachial plexus injury, esophageal perforation, excessive blood loss
Facelift	Early identification of the recurrent laryngeal nerve No drain required Outpatient surgery Favorable safety profile	Transient great auricular nerve hypesthesia Unilateral surgery

The RFT approach eliminates the risk of brachial plexus injury and requires a smaller extent of dissection than RAT [4, 23]. The shorter operative distance makes intraoperative stimulation of the RLN easier (Fig. 7.6), and the reduced dissection volume permits safe outpatient surgery without the need for a drain. RFT, therefore, combines many of the advantages of minimally invasive thyroid surgery with the superior cosmetic results inherent in remote access surgery. RFT does result in transient dysfunction of the great auricular nerve, and due to the vector of approach, it is only appropriate for unilateral surgery (Table 7.1).

Current Considerations in Remote Access Robotic-Assisted Thyroid Surgery

Remote access robotic thyroid surgery has remained popular in many Asian countries, but the enthusiasm in Western practices has been tempered by a number of factors. As with all new medical devices or procedures, the long-term viability of robotic technology in thyroid surgery will depend on a careful and critical evaluation of patient outcomes and safety and is subject to financial and accessibility considerations.

Safety

Patient safety will be the paramount determinant of the future of robotic-assisted thyroid surgery. While no serious complications have been reported with the RFT approach, the RAT procedure has been associated with a number of dramatic complications not usually encountered in thyroid surgery. These have included tracheal injury, arm paralysis, prolonged shoulder pain, esophageal injury, and excessive blood loss [1–3, 11].

It is well documented that outcomes in thyroid surgery are contingent upon the experience of the thyroid surgeon [26, 27]. Surgeons in Asia had over 10 years of experience with endoscopic transaxillary thyroid surgery before they introduced the robotic system. In the United States there was no transition period from anterior cervical to robotic-assisted remote access approaches, so some of these outcome differences may reflect the fact that Western surgeons experienced a learning curve their Asian counterparts completed a decade earlier.

Another important factor in the difference between the Asian and Western outcomes is the difference in both the patient population and the extent of the disease treated in these respective regions [1–3, 28–30]. In the United States, 60 % of the population is overweight or obese, while in Korea 60 %

of patients have a normal body mass index (BMI) [1]. Body habitus is associated with outcomes in RAT, with most authors reporting increased operative time and complications in obese patients [1–3]. Patients in the West also tend to present with a greater volume of disease than patients in Asia. In Korea, where a national system of screening ultrasound examinations results in the detection of microscopic thyroid disease, the average nodule size at surgery is 0.8 cm with a mean thyroid volume less than 10 mL [30]. In Western practices the mean nodule size usually exceeds 2.5 cm with thyroid volumes that regularly exceed 20 mL [30]. Future studies controlling for these differences will be crucial in determining the exact relationship between these variables and surgical outcomes.

Patient Demand

Another hurdle facing robotic-assisted thyroid surgery in the United States is patient awareness and demand. Asian skin is subject to poor wound healing and hypertrophic scarring [31, 32]. In South Korea and other Asian cultures, the cervical region is considered to be an erogenous area, and a scar on the breast is more acceptable than one on the neck [8]. Given these two factors, there is a cultural bias toward remote access thyroid surgery. In the West, however, there is no generalized social stigma associated with this scarring. In a recent survey of 596 patients in Europe who had undergone conventional thyroid surgery, 88 % of patients were satisfied with the anterior cervical approach, and only 12 % of participants would have preferred a remote access axillary method [33].

Despite these findings, some individuals are highly motivated to avoid a visible neck scar. In the Linos study, those patients who would have preferred an axillary approach were younger or had incisions which healed poorly [33]. The interest in remote access approaches among younger patients was confirmed in a random survey of individuals in the United States [34]. Participants with no known thyroid disease were interviewed in random public locations about their surgical preferences for thyroid surgery. Of the 811 respondents, 82 % preferred a hidden remote access incision over an anterior cervical incision if all conditions were equal. A surprising 51 % of patients were willing to have an axillary approach even if there was an increased risk of complications with this procedure. When asked if they would pay an additional $5000 for the procedure, 84 % of respondents would opt for a cervical approach, suggesting that a remarkable 16 % of individuals felt that avoiding a cervical scar was worth this extra cost. In a final scenario, participants were told to assume they had thyroid cancer and that transaxillary surgery might not cure their disease. Given this condition, an astonishing 20 % of patients would still "definitely" or "probably" proceed with the axillary approach. These patients tended to be young females who rated scar appearance as being an important outcome. Though there are a number of limitations with this sort of survey, it does show that while most patients consider multiple factors when making medical decisions, there is a small subset of primarily young female patients who place paramount importance on avoiding a neck scar in thyroid surgery. It is this group that is most likely to seek out remote access robotic thyroid surgery and be willing to tolerate important potential disadvantages of these procedures.

Training and Credentialing

Consideration must be given to the issue of which surgeons should perform advanced and innovative thyroid procedures. There is no formalized pathway for robotic-assisted thyroid surgery training. Individual hospitals are free to determine the requirements for robotic surgery credentialing, and there are no uniform criteria for measuring or monitoring a surgeon's proficiency and outcomes with these techniques.

There is general consensus that proficiency in conventional thyroid surgery is a prerequisite before embarking on a robotic-assisted thyroidectomy program [35]. The endocrine surgery experience is limited in many residency programs [36, 37], so training is usually focused on anterior cervical approaches rather than remote access techniques. Therefore, it is doubtful that these techniques can be acquired during a surgical residency.

There is a significant learning curve in robotic-assisted thyroid surgery. For surgeons highly experienced in transaxillary endoscopic thyroidectomy approaches, the operative time for RAT plateaus at approximately 45 cases [11]. Given that the majority of thyroid surgery in the United States is done by low-volume surgeons, and given the limited number of patients who are candidates for these procedures, surgeons outside of specialized centers will be unlikely to have a consistent caseload high enough to acquire and maintain proficiency with these techniques.

Availability

The widespread adoption of robot-assisted thyroid surgery remains limited by availability. The robotic surgical platform is installed in only a limited number of US hospitals, meaning the majority of patients and surgeons may not have access to the technology. In 2011 the only manufacturer of the surgical robot announced it would no longer support activities related to robotic-assisted thyroid surgery pending further review by the US Food and Drug Administration (FDA) [18, 36]. The robotic system is FDA approved for general surgery applications, although there is no specific endorsement at this time for its use in thyroid surgery.

Indications and Disease Considerations

The optimal use and limitations of robotic thyroid surgery are not yet fully defined and continue to evolve. While clear indications have been published for RFT [25], there are no rigid selection criteria for RAT. The RAT allows limited access to the contralateral lobe through a single axillary incision, theoretically permitting a subtotal thyroidectomy. For practical purposes, however, both the RAT and RFT are most appropriate for patients requiring unilateral surgery.

RAT has been used to treat very small, well-differentiated thyroid malignancies (mostly papillary microcarcinomas) [11, 38]. Some authors have described comparability with open surgery; a systematic review comparing RAT patients with open thyroidectomy patients showed no difference in the postoperative thyroglobulin (Tg) levels between these two groups [39]. Postoperative Tg levels less than 1 ng/mL were achieved in 92 % of patients in one study, with a mean Tg level of 4.9 mg/mL in the remaining 8 % [11]. In another study, there were no abnormal ^{131}I uptake levels in patients undergoing total thyroidectomy by RAT followed by postoperative radioactive iodine therapy [38], though patients undergoing RAT have been reported to have higher postoperative Tg levels than patients having conventional surgery prior to radioactive iodine ablation [40]. Both central and lateral neck dissections have been performed with this approach [41].

Unanticipated findings of malignancy have been reported after unilateral thyroid lobectomy with the RFT approach [24, 25], and these were all treated with completion surgery using the same remote access technique via a contralateral approach, per the patient preference. However, the use of this approach specifically for the treatment of thyroid cancer has not been rigorously evaluated, and this technique is currently reserved for thyroid lesions that are benign or of indeterminate cytopathology that are amenable to unilateral surgery [25]. No cases of central or lateral neck dissection have been reported with RFT.

Resource Utilization

Resource utilization is a concern in robotic-assisted thyroid surgery. RAT, for example, is significantly (1.5 times) more expensive than conventional thyroid surgery [36, 42]. According to some modeling, this cost difference does not resolve until the RAT operative time is reduced to 68 min [42], an outcome that has not been achieved consistently in published series.

By contrast, while no cost analysis has been performed for the RFT procedure, in a small series comparing RAT to RFT, the operative time was lower for RFT [4]. Since much of the increased cost associated with robotic thyroid surgery relates to the operative time, the

incremental expense of RFT should be more modest. Furthermore, RFT is accomplished without need for a drain and on an outpatient basis, essentially erasing any cost differential associated with open surgery. In addition to material costs, there are also operating room costs associated with robotic-assisted thyroid surgery. Every published analysis shows that these procedures take longer to perform than conventional thyroid surgery [2, 42]. However, those publishing on the subject are high-volume, specialized thyroid surgeons who are comparing their robotic times against their own conventional operative times. A final comment should be made when considering costs. While a given surgeon may be able to perform open surgery faster than remote access techniques, it is probable that high-volume experts may accomplish remote access procedures faster than an occasional surgeon completes open surgery. For example, with an average duration approaching 2 h [2, 24, 38, 42], these procedures likely take no longer than a conventional procedure in a community setting. Considering that patients will live with either a visible neck scar or a hidden remote access scar for the rest of their lives, the extra time in the operating room may be justifiable for those individuals who place paramount importance on the cosmetic outcome of the procedure.

Reimbursement

Along with questions of cost are issues of reimbursement. In South Korea, there is significant financial incentive to perform robotic thyroidectomy. These procedures are reimbursed at four times the rate of conventional thyroid surgery [8, 30]. In the United States, however, hospital and physician reimbursement is based on the extent of the thyroid surgery, not the manner in which it is performed. Costs for robotic surgery are higher, to whatever extent the surgery is longer than an anterior cervical approach. As health-care delivery changes, surgeons, insurers, and patients will need to reach agreement about how cost differences and reimbursement patterns associated with robotic-assisted thyroid surgery will be addressed.

Conclusion

Robotic-assisted remote access thyroid surgery offers patients an opportunity to avoid a visible neck scar. The initial enthusiasm of early Western advocates of these techniques, particularly the axillary approach, has been tempered by a number of factors. Rigorous guidelines are required to ensure that patients are optimized for surgical success and that the most appropriate procedure is implemented. Formalized training is needed to ensure that surgeons are qualified to perform safe, efficient operations. Finally, questions of cost and reimbursement should be addressed to ensure economic viability.

It is likely that RFT will supplant RAT as the remote access robotic thyroidectomy procedure of choice in the United States, due to numerous technical considerations and the initial experiences with each approach. Robotic thyroid surgery will likely evolve as a niche operation, performed in academic or specialty practices on highly selected patients who place a high premium on avoiding a visible neck scar. If the resources and technical expertise are available, it is reasonable that these patients should be given the opportunity to achieve their dual goal of disease treatment and a scar-free neck if it is safe and feasible to do so.

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Graves' Disease: What Is the Role and Timing of Surgery?

8

Dawn M. Elfenbein and Rebecca S. Sippel

Can the thyroid gland when in the state of enlargement be removed…? If a surgeon should be so foolhardy as to undertake it…every step he takes will be environed with difficulty every stroke of his knife will be followed by a torrent of blood and lucky it would be for him if his victim lives long enough to enable him to finish his horrid butchery. No honest and sensible surgeon would ever engage in it!

—Samuel Gross, 1848

Graves' disease (GD) is the most common type of hyperthyroidism in the United States, accounting for up to 80 % of cases of hyperthyroidism [1]. The overall prevalence of hyperthyroidism is approximately 1.2 % in the United States [2]. Graves' disease disproportionately affects women, with an annual incidence of up to 80 per 100,000 women, which is ten times higher than in men [3]. Originally defined as a triad of hyperthyroidism, goiter, and ophthalmopathy, Graves' disease today is known to be an autoimmune thyroid condition where circulating thyrotropin receptor antibodies cause unregulated stimulation of the thyroid gland, hypertrophy of the thyroid follicular cells, and overproduction of thyroid hormone. Hyperthyroidism may be the only manifestation of the disease, which can lead to significant skeletal, cardiovascular, and psychological adverse effects [4–6]. These circulating autoantibodies can also cause extra-thyroidal manifestations such as pretibial myxedema and ophthalmopathy. Graves' ophthalmopathy affects 25–50 % of patients with GD, and up to 5 % of patients may have their eyesight threatened [7].

Three effective treatment options exist: antithyroid medications such as methimazole or propylthiouracil, radioactive iodine ablation (RAI), and surgical thyroidectomy. Only one randomized clinical trial has been performed directly comparing these three treatment modalities and concluded that they are all effective at eventually achieving a euthyroid state [8]. The three treatment modalities carry unique risks and benefit profiles, have variable time courses of antibody resolution and achieving euthyroidism, have differences in relapse rates, and can alter the management of complications related to GD such as ophthalmopathy [8]. The current published and accepted guidelines for the treatment of hyperthyroidism [2] stress the importance of active discussion between patients and providers regarding the logistics, benefits, speed of recovery, drawbacks, side effects, and costs of treatment (Table 8.1). The type of treatment selected is very important to the individual patient, as two of the treatments—RAI and thyroidectomy—render most patients permanently hypothyroid and dependent on the medication levothyroxine to maintain a euthyroid state for the rest of their lives. Many important clinical

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Table 8.1 Factors for providers and patient to consider for GD treatment options

	Antithyroid medications	Radioactive iodine	Total thyroidectomy
Logistics	Daily medication	One time treatment, radiation precautions for 1–2 weeks after	Outpatient surgery
Benefits	Noninvasive No radiation exposure	Permanent treatment option without surgical risk	Quickest, most predictable time course for cure
Speed of recovery	1–2 weeks after starting medications, but can take time to regulate dose	Hypothyroidism occurs anytime from 1 to 6 months after treatment	1–2 weeks from surgery, can start thyroid replacement immediately and avoid hypothyroid symptoms
Drawbacks	Highest relapse rate [17]	Variable time course: difficult to predict when to start thyroid replacement. Persistence of antibodies. Radioactivity isolation precautions necessary	Most invasive, requires general anesthesia and surgical risk
Side effects	Rare fulminant liver failure, agranulocytosis [70], more common skin rash	Rare risk of secondary malignancy later in life [32, 71] Can exacerbate eye disease [7]	Hypoparathyroidism, damage to nerves controlling voice
Cost	Ongoing costs of continued medications, depends on duration of therapy	Least costly upfront, but provides lowest QALY[a] [52]	Most expensive upfront, but cost-effective in the longer term based on QALY analysis [52]

[a]*QALY* quality-adjusted life-year

factors influence providers' recommendations for treatment modality, and patient preference also plays an important role in selecting the best treatment for an individual patient.

Historically, surgical treatment for GD had been reserved for patients who failed medical therapy or otherwise had a contraindication for medical therapy. A 2011 survey of endocrinologists found that only 1 % would recommend surgery as first-line therapy. RAI, while less popular than it was 20 years ago, is still the most common treatment offered in the United States [9]. A recent surge in the literature on total thyroidectomy as a first-line treatment for GD reflects growing interest in this as a viable first-line treatment modality [10–14]. This is perhaps due to an increasing number of endocrine surgical specialists who perform this procedure routinely with relatively few complications, increasingly as an outpatient procedure with no overnight stay, leading medical endocrinologists who work with an experienced surgeon to recommend surgery as a first-line therapy. This chapter will describe the evolving role of surgery for Graves' disease, will highlight circumstances where thyroidectomy is definitively the treatment of choice, and will discuss controversies in the perioperative management of these patients.

Diagnosis and Manifestations of Graves' Disease

In 1835, Robert James Graves described a disease that presented with goiter, palpitations, and exophthalmos, although Caleb Parry was probably the first to publish about the disease in an obscure journal 10 years prior to Dr. Graves' work [15]. Karl Adolph von Basedow described the disease in 1840 without knowing that it had been described a few years earlier, and in Europe, it is commonly referred to as Basedow's disease. Originally thought to be a derangement of the cardiac and then sympathetic nervous system, we now know that Graves' disease is caused by circulating autoantibodies that mimic the activity of thyroid-stimulating hormone (TSH). Although these autoantibodies are the immediate cause of the manifestations of the disease, the underlying etiology of what causes the synthesis and release of these autoantibodies remains largely unknown. The variability in clinical presentations of the disease and the diversity in response to treatment suggest that complex interactions exist between genetic and environmental factors, ultimately leading to the loss of immune tolerance toward

thyroid-related antigens. Like all autoimmune diseases, Graves' disease tends to cluster in families. Although several genes that play a role in the susceptibility of a patient in developing dysregulation of immunity (HLA-DLR, CTLA4, CD40, PTPN22) or thyroid-specific molecules (thyroglobulin, TSHR) have been identified, no obvious hereditary pattern exists [16]. Graves' disease has the potential to affect almost every organ system as shown in Table 8.2, and patient presentation is highly variable.

With the exception of those rare patients who present with the dramatic onset of complications related to severe, acute thyrotoxicosis, patients generally present with a more gradual onset of the most common symptoms such as nervousness, palpitations, insomnia, or weight loss despite increased appetite. On laboratory evaluation, patients typically have high serum thyroxine (T4) and triiodothyronine (T3) along with an undetectable TSH. These laboratory abnormalities are present in all forms of hyperthyroidism. If hyperthyroidism is present with no obvious clinical features of Graves' disease, further serum testing for TSH receptor antibody (TRAb) can be performed, and/or patients should undergo radioiodine uptake imaging of the thyroid gland. A specific diagnosis of Graves' disease requires biochemical evidence of hyperthyroidism plus at least one of the following: (1) ophthalmopathy

Table 8.2 Clinical manifestations of Graves' disease by system

System	Clinical finding or manifestation
Central nervous system/ psychological	Suppressed TSH Anxiety Decreased concentration and attention Emotional lability Rare Graves' encephalopathy
Constitutional	Weight loss Fatigue Insomnia Nervousness Dysthermia, usually heat intolerance Increased oxygen consumption Reduced fat mass
Ophthalmologic	Eyelid retraction Edema to tissue around the eye Constant stare Dry eyes or sensation of grit or eye irritation Photophobia Double vision Infiltrative ophthalmopathy
Cardiac	Tachycardia Increased contractility, palpitations Widened pulse pressure Increased risk of arrhythmias or heart failure if left untreated
Respiratory	Dyspnea Air hunger
Gastrointestinal	Dysphagia Direct compression from goiter Myopathy causing pharyngeal or esophageal dysmotility Hyperdefecation Diarrhea Increased appetite Reduced total and LDL cholesterol Association with primary biliary cirrhosis and autoimmune hepatitis
Skin/integument	Flushing Sweating Fragile or thinning hair Onycholysis Pretibial myxedema
Musculoskeletal	Proximal muscle weakness Fatigability Hand tremors Increased bone turnover Decreased bone density Increased risk of fractures Rare thyrotoxic periodic paralysis
Hematologic	Lymphadenopathy Rare anemia or pancytopenia
Reproductive	Gynecomastia, erectile dysfunction, and decreased libido in men Oligomenorrhea and decreased fertility in women Pregnancy complications including higher risk of: Miscarriage Poor fetal growth Maternal heart failure or preeclampsia
Endocrine	Goiter Increased secretion of T3 and T4 Dysregulation of calcium homeostasis

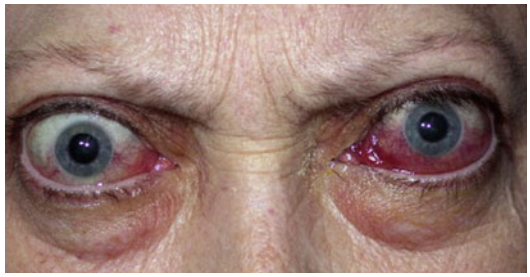

Fig. 8.1 Graves' ophthalmopathy. From Menconi et al. Diagnosis and classification of Graves' disease. Autoimmun Rev. 2014;13(4–5):398–402, with permission of Elsevier

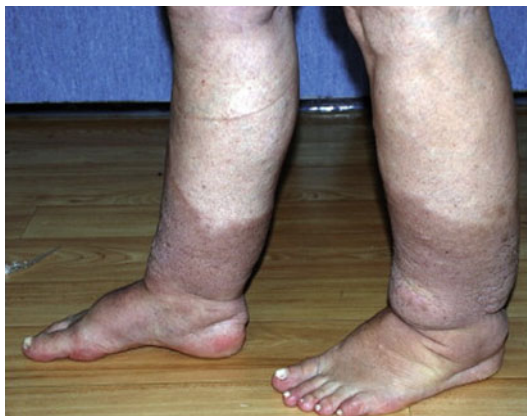

Fig. 8.2 Pretibial myxedema. From Menconi et al. Diagnosis and classification of Graves' disease. Autoimmun Rev. 2014;13(4–5):398–402, with permission of Elsevier

(Fig. 8.1) or obvious dermopathy of Graves' disease such as pretibial myxedema (Fig. 8.2), (2) detectable serum TRAb, or (3) diffuse, increased thyroid uptake on a radioiodine scan.

Goals of Treatment

Once the diagnosis of Graves' disease is established, treatment must be tailored to each individual patient, based on both clinical manifestations of the disease and the personal preferences of the patient. Unfortunately, no treatment yet exists that is able to specifically target the underlying autoimmune condition, and treatment is aimed at correcting the end-organ thyroid dysfunction. With rare exception, patients should initially be started on antithyroid medication (methimazole, except in the first trimester of pregnancy when propylthiouracil is used) at the time of diagnosis to restore euthyroidism [2]. Euthyroidism is usually reached in 6–8 weeks, although patients often start to feel better much sooner than that. Maintenance of euthyroidism is the ultimate goal and can be achieved by one of three strategies: (1) long-term course of antithyroid medication, (2) radioactive iodine ablation (RAI), or (3) surgical thyroidectomy. Radioactive iodine and surgical thyroidectomy destroy the thyroid gland, and almost all patients end up with hypothyroidism that must be treated in the long term with levothyroxine. The other goals of treatment should include minimizing risk to the patient and appropriately treating extra-thyroidal manifestations of the disease, the main one being ophthalmopathy. Appropriate referral and consultation with an ophthalmologist should be made if eye symptoms are present. The main focus of the remainder of this chapter will be strategies to achieve and maintain euthyroidism while minimizing risks to the patient in the modern era.

The majority of clinicians in a recent survey in Europe (85%) and a large portion of clinicians in the United States (40%) responded that for a patient with uncomplicated Graves' disease, a course of methimazole is the preferred treatment modality [9]. Antithyroid medications have a favorable risk profile, but unfortunately carry the highest risk of recurrence (over 50 %) after stopping the medication [17]. In that same survey, 59 % of clinicians in the United States felt that RAI is the preferred treatment, leaving only 1 % who chose surgical thyroidectomy as the preferred treatment for uncomplicated Graves' disease. Surgery is the most invasive, carries the highest immediate risk profile of the three modalities, and therefore traditionally has been reserved for special situations including finding suspicious thyroid nodules in the setting of Graves' disease, young age (including pediatric patients), failure of RAI, pregnancy, medication side effects, compressive symptoms and/or large goiter, or severe Graves' ophthalmopathy, among others [12, 18]. In short, in the absence of extenuating circumstances, surgery traditionally

was viewed as too risky to be offered as a first-line therapy.

In the past 15 years, however, several large shifts have occurred that have started to change the way some clinicians and patients are thinking about the treatment of Graves' disease. First, there has been an increased focus on the delivery of patient-centered medical care that prioritizes communication and an integrated understanding of patient preferences with regard to their unique situation [19]. Gone are the days of paternalistic medicine where a clinician decided for a patient what the best course of treatment should be. Second, the exponential rise in websites and media coverage that may or may not contain accurate medical advice may contribute to an increased fear about radioactivity [20, 21] Third, due to increased awareness of the potentially life-threatening complications of antithyroid drugs, especially propylthiouracil (PTU), there has been a shift away from using this drug, particularly in children [22, 23]. Finally, in 2005, the American Association of Endocrine Surgeons ratified a formal fellowship curriculum that now includes 23 accredited programs in North American programs in 2014 [24]. High-volume endocrine surgeons have superior outcomes after thyroid surgery [25], and fellowship-trained endocrine surgeons are joining community practices and becoming faculty at academic institutions across the country, increasing access to high-volume thyroid surgeons in many areas. Because of these shifts, perhaps now is a good time to more closely scrutinize all three treatment modalities and reexamine the risk, benefit, and cost profiles for each.

Antithyroid Medications

Antithyroid medications are effective at quickly reducing the production and conversion of thyroid hormone. Antithyroid medications do not cure the underlying etiology of Graves' disease, though, and their major role is for the maintenance of euthyroidism until a spontaneous remission occurs. Remission occurs in 20–30% of patients after a 12–18 month course of medication and 50–60 % after 5 years of treatment. Rates of remission are lower in men, smokers, those with large goiters, those with persistently elevated TRAb levels while on treatment, and those with high thyroid blood flow on Doppler ultrasound [2].

Propylthiouracil (PTU) used to be the favored antithyroid drug, but concerns about potentially fatal, fulminant, hepatic necrosis have limited its use today. The FDA issued a safety warning in 2009, noting 22 adult and ten pediatric cases of serious liver injury associated with the drug [26]. For this reason, its use is now limited only to patients in the first trimester of pregnancy due to teratogenic effects of the alternative drug, methimazole. Methimazole and its precursor drug, carbimazole (not available in the United States), work by inhibiting the enzyme thyroperoxidase, thus preventing the iodinization of thyroglobulin and decreasing the production of both T3 and T4. Methimazole also can cause hepatotoxicity, but this is usually cholestatic and not fulminant hepatocellular damage as seen in PTU therapy. A rare but serious side effect of both methimazole and PTU is agranulocytosis, which can lead to neutropenic fever and serious illness. Patients on either drug need baseline and periodic complete blood count and liver function tests. Methimazole can be effective when given once a day, but higher doses are sometimes needed to achieve euthyroid levels, and side effects increase in a dose-dependent manner. Minor side effects, such as skin rash, joint pain, gastrointestinal symptoms, and changes in taste (PTU has a strong metallic taste) can be seen in around 15 % of patients taking antithyroid medications.

Because antithyroid medication treatment provides the possibility of remission without the destruction or removal of the thyroid gland (unlike RAI and surgery), patients with a strong aversion to treatment that will render them permanently hypothyroid with a subsequent lifelong dependence on levothyroxine should consider this treatment option. Patients with serious comorbidities that would make surgery unacceptably high risk or patients who have had high previous radiation exposure making RAI higher risk should also consider this option [2]. However, patients who are looking for a definitive and rapid

treatment option may be frustrated by the low remission rate, the frequent blood draws for monitoring, and the potential—albeit rare—for serious side effects.

Radioactive Iodine Ablation

Radioactive iodine (^{131}I) is administered orally in a one time dose with a goal of rendering a patient euthyroid, but most often results in hypothyroidism. Iodine is a necessary and essential precursor in thyroxine synthesis, and ^{131}I is taken up by the iodide transporter of thyroid cells. The radioactive particles then destroy the follicular cells from the inside. The effectiveness of the treatment depends largely on how much radiation is deposited into the actual thyroid gland, which depends on the dose administered, the size of the thyroid gland, and the ability of the follicular cells to trap iodine. Both the size of the thyroid and the ability of the cells to take up iodine can vary widely among patients, and even with careful dose calculation taking into account some of these differences, the failure rate of a single dose of RAI can be 12–21 % [13, 27]. In those failing to respond to one dose, RAI may be repeated, or patients may choose to undergo one of the other two treatment options. Failure rates may be higher in men, younger patients [18], and those with large goiters [28]. High failure may be predicted in patients with high T4 levels or those who first undergo treatment with methimazole [29]. Pregnancy or desire to become pregnant within 6 months is an absolute contraindication to RAI due to the risk of the baby being born without a thyroid gland and other risks of radiation to the fetus; lactation and inability to comply with radiation safety guidelines are also contraindications [30].

Because RAI involves ingesting a radioactive isotope, it exposes the individual to radiation, particularly in organs involved in the absorption, concentration, or excretion of iodine, namely, the stomach, thyroid, breast, salivary glands, and kidneys. An individual patient's cumulative exposure to radiation depends on many factors, including dose of ^{131}I, the mass of the thyroid gland, and renal function. Patients with Graves' disease often receive much lower doses of ^{131}I than patients who are receiving an ablative dose after thyroidectomy for thyroid cancer, but because they still have their thyroid gland in place and it is hyperfunctioning and often enlarged, these patients sequester more radioactivity in the thyroid gland and have high levels of circulating radioiodinated thyroid hormones than patients with cancer [31]. Compared to normal controls, patients who received RAI in one Finnish study of 2793 patients showed higher relative risk of cancer after a 5-year latency period, particularly cancer of the stomach, kidney, and breast. [32] Other studies have demonstrated mixed results, with some finding increased cancer risk but others finding none [30]. The same Finnish group reported higher cardiovascular morbidity and more hospital admissions due to atrial fibrillation, cerebrovascular disease, hypertension, and heart failure, as well as higher admissions for infections, gastrointestinal diseases, and fractures in patients with Graves' disease treated with RAI [33]. It is difficult to discern whether hospitalizations are a consequence of RAI or of hyperthyroidism, since the patients were compared with healthy controls instead of to patients with Graves' disease treated with surgery or antithyroid medications. A long-term, prospective study of patients treated with all three modalities is needed to help patients and providers understand the long-term effects of treatment and aid in decision-making.

The most studied aspect of RAI therapy has been the effect of the treatment on ophthalmopathy. Unlike treatment with antithyroid medications and surgery, where levels of circulating autoantibodies decrease when treatment is initiated, ^{131}I treatment actually causes a surge and sustained increase of circulating antibodies as thyroid tissue is slowly destroyed (Fig. 8.3). This surge in antibodies can worsen existing ophthalmopathy or even result in the development of eye disease in patients who had no eye complaints prior to treatment. Patients who smoke cigarettes are at higher risk of worsening ophthalmopathy, and steroid treatment prior to the administration of ^{131}I has been shown to prevent this worsening of eye disease [34]. Although not listed as a true

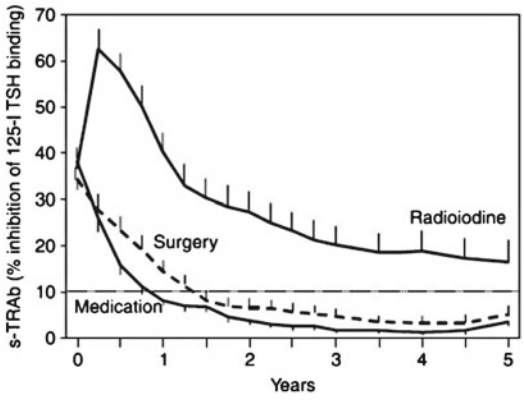

Fig. 8.3 Resolution of antibodies with treatment of Graves' disease. From Laurberg et al. TSH-receptor autoimmunity in Graves' disease after therapy with antithyroid drugs, surgery, or radioiodine: a 5-year prospective randomized study. European Journal of Endocrinology. 2008;158(1):69–75, with permission of Bioscientifica Ltd

contraindication, patients with severe ophthalmopathy or patients who have ophthalmopathy and smoke should be counseled that the risk of worsening or development of ophthalmopathy is around 20 %, and many providers think about other treatment modalities first over RAI in these patients.

While the goal of treatment is to achieve a euthyroid state, the reality is that most patients who receive RAI become hypothyroid and require lifelong levothyroxine. Patients almost always trade one disease for another—hypothyroidism—and it can be quite challenging to predict when an individual patient will cross over from one to the other. Euthyroidism, and then subsequent hypothyroidism, may occur anytime between 4 weeks and 6 months after taking a dose of ^{131}I, but in one large study, 24 % of patients became hypothyroid in the first year, 59 % were hypothyroid after 10 years, and 82 % were hypothyroid after 25 years of follow-up [35]. Predicting the time that a patient becomes hypothyroid is difficult, and starting levothyroxine too early can exacerbate hyperthyroidism symptoms, while waiting too long to start the medication can result in a period of symptomatic hypothyroidism and distressing symptoms such as weight gain and fatigue. Frequent blood tests to monitor thyroid function are necessary, and even with frequent monitoring, symptoms of hypothyroidism can develop at any time after treatment.

Side effects directly attributable to RAI therapy are rare, but when present can be life-altering. Sialadenitis, or inflammation of the salivary glands, can occur with treatment. In the acute phase, this can lead to painful swelling of salivary glands. In the chronic form, this can cause dry mouth and alterations in taste that can be permanent. Lacrimal duct stenosis and obstruction, as well as decreased tear production, can also occur, previously thought to be dose dependent and in patients who receive higher doses for thyroid cancer, but more recently found to occur at lower doses for Graves' disease patients [36]. Rarely, patients can experience acute, painful thyroiditis that can last days to weeks after ingesting ^{131}I and may require steroid treatment. Finally, patients are advised to follow radiation safety guidelines for several days after therapy, maintaining safe distance (usually around 6 ft) from other adults and even further distance from children and small animals. While this can be inconvenient for most patients, those who are the sole caregivers to small children or pets may find this impossible and may opt for other treatment options.

Thyroidectomy

For patients who find that a recurrence rate of 40–80 % with antithyroid medications is too high or who worry that the conversion to hypothyroidism after RAI is too unpredictable, total thyroidectomy followed immediately by initiation of levothyroxine therapy offers an attractive third choice. Once only offered to patients with unique clinical features, such as pregnancy, severe ophthalmopathy, suspicion for malignancy, or medical/RAI treatment failure, patient preference for a fast and definitive treatment has now become a widely accepted indication for surgery as a primary treatment for Graves' disease. In the United States and other countries where levothyroxine is readily available, total thyroidectomy is preferred over subtotal thyroidectomy due to the fact that, in

experienced hands, it carries similar complication rates to a less than total excision, and it carries a recurrence rate of practically zero [12, 37–39].

In countries or populations where access to levothyroxine is not readily available or where an experienced thyroid surgeon is not accessible, subtotal thyroidectomy may be the most appropriate surgical treatment. Subtotal thyroidectomy leaves remnants of thyroid tissue (2–3 g on each side) posteriorly around the area of the insertion of the recurrent laryngeal nerve. Leaving thyroid intact in this location leads to less possibility of injuring the nerve at its most vulnerable location, which is its point of insertion near the ligament of Berry. It also protects the parathyroid glands along with their blood supply. In theory, this remaining thyroid tissue should function normally, but it is quite difficult to estimate exactly how much thyroid tissue is required for an individual patient. One study reported that subtotal thyroidectomy was associated with higher blood loss and longer hospital stays over total thyroidectomy, and still over 70 % of the patients receiving a subtotal thyroidectomy ultimately required levothyroxine replacement due to inadequate function of the remaining tissue [38]. A recent meta-analysis of 3242 patients from four randomized controlled trials and 19 high-quality non-randomized comparative studies from 1970 through 2012 found that subtotal thyroidectomy was associated with a tenfold higher risk of recurrence of hyperthyroidism over a total thyroidectomy. However, total thyroidectomy did have an increased risk of both temporary and permanent hypoparathyroidism over subtotal. The risk of recurrent laryngeal nerve palsy was no different [40]. In a separate meta-analysis, looking only at the 674 patients in the four randomized trials, none of which were earlier than the year 2000, rates of temporary hyperparathyroidism were still higher, but there was no increase in permanent hypoparathyroidism for total thyroidectomy [41]. Some of the temporary hypocalcemia after surgery could be attributed to the fact that Graves' disease itself plays a role in calcium metabolism, and one recent study suggests that pretreatment with calcium carbonate decreases the incidence of symptomatic hypocalcemia in the postoperative period [42].

The underlying inflammation of the thyroid gland in Graves' disease makes it a more technically challenging operation than thyroidectomy for other indications, such as nontoxic nodular goiter [43]. As has been demonstrated for a variety of surgical procedures, there is a positive relationship between volume and outcomes for thyroidectomy. In one large analysis of the Healthcare Cost and Utilization Project Nationwide Inpatient Sample (HCUP-NIS), for high-volume surgeons (defined as more than 100 thyroid operations per year), there was no increase in complications when a thyroidectomy was performed for Graves' disease. However, for low- and intermediate-volume surgeons, Graves' disease as the indication for thyroidectomy increased the odds for any complication—including hypocalcemia and vocal fold paralysis—by 39 % and 34 %, respectively, compared to thyroidectomy for other benign or malignant thyroid disorders [25]. There is projected to be continued growth in endocrine surgery positions, particularly at academic centers [44], and improved access to fellowship-trained, high-volume endocrine surgeons may allow patients who prefer this rapid and effective treatment to undergo it safely and through relatively small incisions (Fig. 8.4).

The technical aspects of thyroidectomy for Graves' disease are not different than thyroidectomy for other indications such as cancer or goiter, but the vascularity and friability of the gland can make it challenging. Remembering a few important pearls when operating on a patient with Graves' disease can reduce both surgical complications and recurrence rates. In any patient with hyperthyroidism, it is important to be vigilant about the presence of a pyramidal lobe and to resect it in its entirety to reduce a patient's risk of recurrence. The inflammation of the gland can make parathyroids difficult to see, and they can become densely adherent to the thyroid gland. The overall higher vascularity of a thyroid gland with Graves' disease makes it challenging to identify and preserve the blood supply to the parathyroids. A close capsular dissection should be done to best preserve the parathyroid gland, particularly the lower glands that can be quite variable in the anatomic location. After the thyroid gland has been removed, it should be carefully

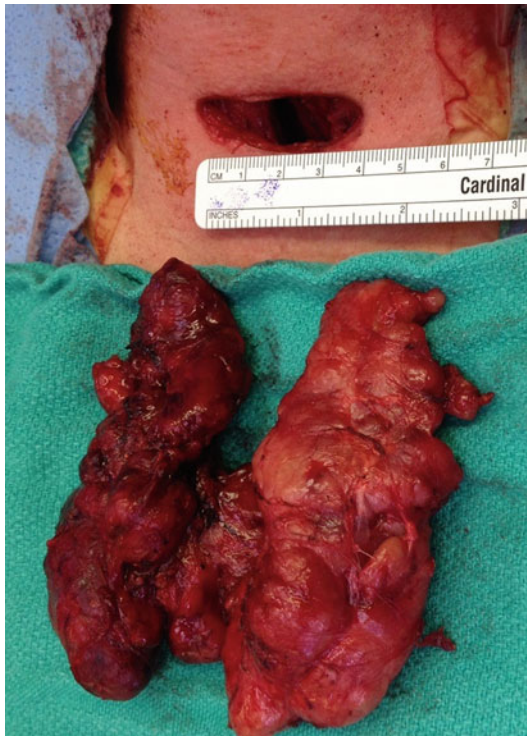

Fig. 8.4 Surgical thyroidectomy (original image, Dawn Elfenbein)

examined to ensure that no parathyroid glands were inadvertently removed. If a parathyroid gland is inadvertently removed or its blood supply is compromised, then the parathyroid gland should be autotransplanted at the end of the case. Finally, the astute surgeon must communicate with the anesthesia team about the possibility of thyroid storm and the manifestations (such as tachycardia) and be able to assist them in the appropriate management of this condition should it occur. It is best to have medications immediately available (beta-blockers—specifically esmolol due to its rapid onset, steroids) in case they are needed.

Special Considerations

While surgical management of Graves' disease is certainly gaining more attention as a viable first-line treatment option for patients with uncomplicated disease, there remain some patients with certain clinical features where surgery offers several distinct advantages that make it definitively the treatment of choice. Any patient with Graves' disease that also has nodular disease that is suspicious for malignancy should undergo surgery for definitive diagnosis. Thyroid nodules are common, and the ATA recommendations for the workup of thyroid nodules are the same regardless of whether patients have an underlying diagnosis of hyperthyroidism. Any nodule >1 cm in size (discovered on physical exam, ultrasound, or a cold nodule on iodine uptake scanning) should be sampled with fine needle aspiration for biopsy [2]. Most nodules in the setting of Graves' disease are benign [45], but patients with cytology-confirmed Bethesda 4 (follicular neoplasm), Bethesda 5 (suspicious for malignancy), or Bethesda 6 (malignant) lesions should undergo surgery instead of medication or RAI, and surgery should be strongly considered for patients with Bethesda 3 lesions (follicular lesion of undetermined significance or atypia). In patients who are euthyroid, unilateral lobectomy is recommended for patients with Bethesda 4–Bethesda 5, and patients with Bethesda 3 lesions are often recommended for a second biopsy after a period of at least 6 weeks [46]. However, these guidelines for unilateral lobectomy or repeat biopsy should not apply to a patient with underlying hyperthyroidism and access to a high-volume thyroid surgeon, since total thyroidectomy will provide tissue for adequate diagnosis while treating the Graves' disease at the same time. Patients with Graves' disease and diffuse enlargement or benign nodules that cause compressive symptoms should also be offered surgery as it will provide the most rapid correction of both problems.

In women who desire pregnancy, there are several reasons why surgical thyroidectomy is the preferred treatment. Methimazole is teratogenic and should not be used in the first trimester of pregnancy, so its use is contraindicated in women who are actively trying to conceive. PTU is an acceptable alternative, but conception is an inexact event, especially in women with hyperthyroidism, so the duration of treatment could potentially be long. Attempts to conceive should not begin for 4–6 months after RAI therapy, which is an unacceptably long time for some women. Furthermore, RAI is known to increase

dramatically the levels of circulating autoantibodies for up to a year after treatment (Fig. 3, from [47]). Circulating thyroid autoantibodies are associated with maternal and fetal complications of pregnancy, including preeclampsia, abruptio placentae, and neonatal thyroid dysfunction [48]. For women who desire pregnancy, thyroidectomy by an experienced surgeon will lower serum autoantibodies as effectively as antithyroid medications and provides more certainty in terms of timing that many women who are already going through a stressful life experience may find appealing. Women who are diagnosed with Graves' disease during pregnancy should usually be managed with antithyroid medications (PTU in the first trimester, otherwise methimazole), unless she personally has had a serious reaction to them in the past. As with any surgery, there is an increased risk of fetal loss during the first trimester and an increased risk of preterm labor in the third trimester, so the second trimester is the preferred time for surgical intervention, if possible.

As discussed earlier in the chapter, patients with severe ophthalmopathy or patients who have ophthalmopathy and smoke cigarettes have the potential for worsening eye disease with RAI, and many clinicians have started to view these as strong indications for surgical treatment [12]. The ATA guidelines recommend that anyone with active moderate to severe or sight-threatening ophthalmopathy be treated with antithyroid drugs or surgery [2]. A final population that deserves special consideration for surgical treatment is children with Graves' disease. An entire chapter could be devoted to Graves' disease in the pediatric population, but here, it is worth considering some of the potential problems unique to children. As with all forms of radiation, children who are growing and developing are more sensitive to the harmful effects of radiation than adults, and their size can make it slightly more challenging to calculate the proper dose of ^{131}I. Furthermore, although exact dosimetry studies are not available, it seems that younger children exposed to equivalent doses of ^{131}I based on weight alone have a higher total radiation exposure than older children or adults [2]. With antithyroid medications, there is no consensus on the duration of treatment, and the rates of remission in younger children seem to be lower than adults [2]. Although it can be high anxiety for parents, children generally tolerate most surgeries well, and it is a safe and effective treatment option when performed by an experienced thyroid surgeon [49]. As with adults, selecting the treatment that is best for the pediatric patient should be highly individualized and involve the patient and caregivers [50].

Costs, Quality of Life, and Access to Care Issues

The group in Sweden that performed the only randomized controlled trial of all three treatment options for Graves' disease performed a follow-up analysis looking at the quality of life and economic impact of the treatment options [51]. They took into account the cost of initial therapy (RAI, surgery, or 18 months of antithyroid medications) as well as the cost of relapses and the number of repeat treatments in the 7 years following randomization. The surgical groups had upfront costs approximately 2.5 times higher than both the medical group and RAI. However, taking into account relapse rates and the cost of second treatments for the almost 50 % of patients who failed medical therapy, surgery was only 1.3 times more expensive than medical therapy. The cost-effectiveness analysis methods used in this study were somewhat simplified and based on hypothetical costs of secondary treatments, but they essentially were the first to show that the higher initial costs of surgery were largely offset by its lower recurrence rates and less intensive long-term follow-up. Patients in all three groups were relatively satisfied with their treatment, and there were no significant differences in satisfaction or whether patients would recommend therapy to a friend among all three treatment options [51].

Since that trial, several groups have performed cost-effectiveness analyses. One group from Boston used a decision-tree model based on a common scenario of initial treatment with 18 months of

antithyroid medications for all patients. The model assumed a 50 % failure rate of medications and assumed patients would go on and either continue medications, undergo RAI, or undergo total thyroidectomy, and the authors assumed published and regularly accepted rates of complications and failure rates for each of the treatments. Costs were calculated using actual Medicare reimbursements to a large urban hospital, and outcomes were measured in quality-adjusted life-years (QALY). The authors concluded that RAI was the least costly treatment option, but provided the least QALY. Although total thyroidectomy added additional cost, it had the highest QALY, making it the most cost-effective strategy for the treatment of Graves' disease after a failed course of antithyroid medication [52]. This study was criticized for using published complication rates for multinodular goiter in the calculations and did not properly take into account the increased rate of hypocalcemia after surgery specifically for Graves' disease. Hughes et al. reported that almost twice the number of Graves' disease patients required calcium supplementation after surgery than patients with multinodular goiter (57 vs. 34 %) and that the increased cost of that treatment may alter the interpretation of cost-effectiveness studies [53]. Other groups have reported much lower hypocalcemia rates that are more similar to thyroidectomy for other indications [10, 11], which highlights the importance of each surgeon tracking his or her own outcomes and honestly discussing these with patients prior to surgery.

One group of surgeons in Australia surveyed 63 patients who underwent surgery for Graves' disease and found that around one third of the patients did not have a specific indication for surgery such as a concomitant thyroid nodule or severe ophthalmopathy. Nearly all of the patients (88%) reported a high level of satisfaction with surgery as their treatment choice [54]. Watt et al. in Denmark developed a disease-specific quality of life survey for patients with benign thyroid disorders (ThyPRO [55]) that was given to 31 patients with Graves' disease and 28 patients with toxic nodular goiter who underwent thyroidectomy in Belgrade. The authors reported that patients with Graves' disease scored lower on this disease-specific quality of life preoperatively, but had significant improvement in all measured domains after surgery [56]. This instrument has not yet been applied to determine if there is a difference in improvement in quality of life after each of the three modalities to treat Graves' disease.

Healthcare disparities may exist in the management of Graves' disease, and further data to better identify disparities and identify effective strategies to reduce or eliminate disparities based on socioeconomic status are needed. Jin et al. in Cleveland found that the 99 patients referred for surgery for Graves' disease from 1999 to 2009 at their institution had lower median income and were more frequently uninsured compared to the 535 patients treated medically [57]. Our own institution found that patients with lower socioeconomic status were more likely to present with manifestations of Graves' disease best treated with surgery, such as large goiter or severe ophthalmopathy, underscoring the need for access to high-quality surgical care for all patients [58].

Management Strategies in the Perioperative Period

Potassium Iodide

Lugol's solution is a solution of iodine and potassium in water that once was used in itself as a treatment for hyperthyroidism. Ingesting large amounts of iodine causes an autoregulatory cascade known as the Wolff-Chaikoff effect that inhibits oxidation of iodide in the thyroid gland, decreasing formation and release of thyroid hormone. It is also felt to reduce the vascularity of the thyroid gland resulting in less blood loss during a thyroidectomy, and therefore, the ATA recommendation is that most patients should be given this in the preoperative setting after rendering a patient euthyroid with methimazole. Recent literature, however, suggests that in the hands of experienced surgeons, outcomes are similar for patients who do not receive Lugol's solution in the preoperative setting [59]. Personal anecdotal

experience has found that although patients with Graves' disease who took Lugol's solution before surgery do seem to have less vascularity at the time of surgery, the thyroid gland can seem more friable, difficult to hold and manipulate, leading to a potentially more difficult dissection. Blood loss during thyroid surgery is almost always minimal, and blood loss requiring transfusion is exceedingly rare, so administering a medication that decreases blood loss at the potential expense of making an operation more difficult needs further investigation.

Preoperative Medications

Thyroid storm is a life-threatening condition where patients with hyperthyroidism acutely decompensate causing multi-organ dysfunction [60]. This can occur when patients who have hyperthyroidism are involved in trauma or other critical illness unrelated to their thyroid, but can also potentially be precipitated by taking a patient with untreated hyperthyroidism to the operating room for a thyroidectomy. Although this is a rare event, most surgeons and anesthesiologists prefer patients to be biochemically and clinically euthyroid prior to induction of general anesthesia for thyroidectomy, and treating patients with methimazole preoperatively is the official recommendation of the ATA [2]. However, in one large series from Nashville, although nearly all patients were pretreated with methimazole, 42 % of 165 patients were still hyperthyroid (as defined by elevated T3 and T4, since suppressed TSH levels can lag behind hormone levels) at the time of surgery. The only difference seen was that patients with moderate or severe hyperthyroidism were more likely to need intraoperative beta blockade, but these patients did not have any increased rates of complications [61]. At high-volume centers, where both surgeons and anesthesiologists are attentive to the intraoperative management of patients with hyperthyroidism, thyroidectomy appears to be safe even in patients who remain hyperthyroid despite treatment with antithyroid medications preoperatively.

Some patients have severe reactions to antithyroid medications or have an otherwise acute presentation like new-onset rapid atrial fibrillation that would make waiting several weeks for antithyroid medications to work undesirable. In these situations, symptomatic control with beta-blockers may be appropriate in lieu of methimazole. Furthermore, elderly patients with symptomatic hyperthyroidism, patients with cardiovascular disease, or any patient with a resting heart rate of over 90 beats per minute should be treated with a beta-blocker medication in addition to methimazole to more quickly decrease heart rate and blood pressure, tremor, emotional lability, and irritability. In high doses, beta-blockers also can decrease the peripheral conversion of T4 to active T3 [2]. Propranolol is the drug most often used in this setting, and dosage can range from 10 to 40 mg three or four times a day and should be started low and titrated up for symptom relief. Propranolol is a nonselective beta-blocker, so may not be well tolerated in patients with moderate to severe bronchospasms due to asthma or other obstructive lung diseases. Atenolol or metoprolol may be better tolerated in these patients. After surgery, beta-blockers should be weaned off slowly as patients become euthyroid and not abruptly stopped. The duration of the taper depends on the magnitude of hyperthyroidism at the time of the operation, and patients who are euthyroid at the time of operation can probably undergo a quicker taper than those who are still hyperthyroid. In our euthyroid patients, we usually cut the beta-blocker dose in half for 1 week and in half again for the next week and then stop altogether by 2 weeks postoperatively.

Although Lugol's solution is used in the preoperative setting to decrease vascularity of the thyroid gland for surgery, caution should be used in giving to patients who are thyrotoxic. Patients who are overtly hyperthyroid may use the initial ingestion of excess iodine as substrate for making more thyroid hormone instead of suppressing its production, so it is generally not advised in a patient who is unable to take antithyroid medications first [62]. High doses of glucocorticosteroids can be used to decrease the peripheral conversion of T4 to active T3 in patients with overt thyrotoxicosis. Hydrocortisone 100 mg every 8 h or dexamethasone 2 mg every 6 h can

be given for 3 days prior to surgery in the overtly thyrotoxic patient for a rapid surgical prep [62].

Calcium metabolism is altered in patients with Graves' disease at baseline, and it is consistently shown that rates of temporary hypocalcemia after thyroidectomy are higher in patients with Graves' disease than in patients with other pathologies. The hyperthyroidism of Graves' disease seems to alter the calcium/PTH set point in patients, and they have an exaggerated release of PTH in response to hypocalcemia [63]. Because of this pre-existing calcium dysregulation, Oltmann et al. hypothesized that preoperative treatment with calcium carbonate would result in fewer episodes of symptomatic hypocalcemia in patients undergoing thyroidectomy for Graves' disease. In this study of 83 patients over a 9-month period, those patients treated with calcium carbonate 1000 mg three times daily for 2 weeks before surgery had higher postoperative calcium levels (8.6 mg/dL vs. 8.3 mg/dL) and fewer complaints of numbness and tingling than those who did not take calcium prior to surgery (9 % vs. 26 %) [42]. Although this was a small, non-randomized trial, this is a low-cost, low-risk intervention that may help reduce symptoms after surgery and should be considered for all patients undergoing thyroidectomy for Graves' disease.

Nerve Monitor

Although it has been extensively studied [64–66], the use of intraoperative nerve monitoring to verify recurrent laryngeal nerve function during a thyroidectomy has not been shown to decrease rates of permanent nerve injury. The most recent meta-analysis of the published literature on the use of intraoperative nerve monitoring did report a decrease in rates of temporary nerve palsy with the use of the nerve monitor [66], but studying these phenomena is challenging. The overall risk of nerve injury is low, so trials have to be large to find a significant difference in outcomes, and significant heterogeneity exists in how surgeons use the monitor making it difficult to interpret and compare studies.

Recurrent laryngeal nerve injuries often are not caused by obvious transection of the nerve, but rather by stretching or traction injury that is impossible to identify visually. Nerve stimulation monitors can detect these types of injuries. Surgeons who use the nerve monitor routinely generally subscribe to the idea that detection of the loss of a nerve signal can alert the surgeon to consider aborting the operation after removing the thyroid lobe and prevent the potentially catastrophic complication of a bilateral nerve injury. Because most injuries of this type are transient, completion thyroidectomy can then be performed once the nerve has recovered. Surgeons who do not use the nerve monitor routinely point out that most temporary nerve injuries identified by loss of signal resolve very quickly, usually in the operating room, and that aborting the procedure and putting the patient through a second operation are not the right approach. One recent study reported that 15 of 16 nerves that lost a signal during a thyroidectomy recovered their signal in a mean time of 20.2 min and only 3 of those 15 nerves were associated with transient vocal cord dysfunction [67].

Most nerve monitoring systems used during thyroidectomy today are intermittent stimulation, meaning they require the surgeon to stop operating, pick up a device that stimulates the nerve, touch this device to the recurrent laryngeal or vagus nerve, and then listen for a tone or look for a signal amplitude spike on a monitor. Critiques point out that this type of system can only identify an injury after it has occurred. An ideal system would alert a surgeon just before an injury occurs, so that the surgeon can stop doing whatever he or she is doing that is putting the nerve at risk of injury. There is a device that continuously stimulates the vagus nerve throughout surgery, and one recent study reported that this device can reliably signal impending nerve injury and allow the surgeon to initiate corrective action and prevent the injury [68].

Rigorous testing and cost-effective analysis of these types of monitors have not been done, and no consensus guidelines yet exist regarding the use of nerve monitors. Surgeons must decide for themselves whether it is a useful adjunct, and some surgeons use the monitors selectively for difficult or re-operative cases. There is a learning curve to these monitoring systems, and they

require the ability to troubleshoot problems with the machine itself. Using a monitor routinely may have the advantage that the surgeon learns to manage the problems that may cause a false-positive loss of signal during routine cases (endotracheal tube positioning, setting changes on the machine, grounding wire misplacement, etc.). Getting over this learning curve during routine cases can provide some confidence when using the monitor in more challenging cases where it can help in the identification of a nerve in a field full of scar tissue, while a surgeon who only uses the nerve monitor during difficult cases may be less confident that a loss of signal indicates true injury versus mechanical malfunctions.

Postoperative Levothyroxine

If a patient is euthyroid at the time of thyroidectomy, levothyroxine may be started the day after surgery. One advantage of surgery over RAI is that the exact time that a patient's native thyroid hormone production stops is known—down to the minute—and as long as levothyroxine is started right away, patients should theoretically have no period of hypothyroidism. Levothyroxine is usually dosed by body weight, but we found that a simple weight-based calculation can overestimate thyroid hormone needs in obese patients and underestimate needs in underweight patients. We use a body mass index (BMI)-based algorithm that provides a simple way to calculate estimated dose that seems to more accurately dose levothyroxine for patients after thyroidectomy [69]. In patients who are hyperthyroid at the time of thyroidectomy—assessed by the presence of clinical symptoms or hyperthyroidism and/or T4 and T3 levels, not simply suppressed TSH as it lags behind other lab values by a few weeks—a surgeon may choose to wait 5 days before starting a patient on replacement levothyroxine. The half-life of T4 is 5–7 days, so waiting for one half-life for circulating levels of T4 to fall after surgery may be appropriate.

To determine if the patient is on the correct dose of levothyroxine, serum TSH and T4 should be checked around 6–8 weeks postoperatively. This time lag allows for all residual thyroid hormone to clear and for the labs to accurately reflect the chosen dose of levothyroxine. Because TSH can sometimes lag behind free hormone levels for up to a month or two, we do recommend checking T4 levels in addition to TSH in this patient population. Checking labs sooner than 6 weeks can be challenging to interpret and should be avoided unless patients are manifesting overt signs of hyper- or hypothyroidism. Although overt hyperthyroidism is quite unpleasant with tremors, anxiety, and significant symptoms, mild hyperthyroidism may actually be well tolerated and preferable to some—patients may feel energetic and stay thin without exercising. The astute surgeon should realize that many patients with Graves' disease may have been living with mild hyperthyroidism for some time before surgery and have adjusted to this new normal. Postoperatively, if a patient has a TSH on the high end of normal, they may feel tired or complain of weight gain, and a slightly lower TSH goal (usually around 1 mIU/L) may be best for these patients.

Conclusions

Surgery is becoming a more widely accepted first-line treatment option for patients with Graves' disease, as total thyroidectomy by an experienced thyroid can be performed with low complication rates and excellent outcomes in terms of disease recurrence. Patient preference has long been recognized as an important part of the decision about which treatment to pursue, particularly since three relatively equally efficacious options for Graves' disease exist. Ultimately, patients themselves need to weigh all the risks and benefits of the treatment options and decide for themselves, but providers who treat patients with this disorder have a responsibility to remain up to date on changing outcomes of each treatment and to fully inform patients about all the options.

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Vocal Fold Paralysis and Thyroid Surgery

9

Michael S. Benninger and Joseph Scharpf

Incidence and Prevalence of Vocal Fold Paralysis

Vocal fold paralysis is a common disorder resulting in changes in voice and swallowing. A large series of 827 patients followed for 20 years has shown that there has been a gradual change in the etiology of vocal fold paralysis (Tables 9.1 and 9.2) [1]. Traditionally, extralaryngeal malignancies and iatrogenic injury, principally thyroid surgery, were the most common causes of both unilateral and bilateral vocal fold paralysis. Over time vocal fold injury remained most commonly associated with a surgical procedure (37 %); however, non-thyroid surgeries (66 %), such as anterior cervical approaches to the spine and carotid endarterectomy surgery, surpassed thyroid surgery (33 %) as the most common iatrogenic cause. Thyroidectomy continues to be the most common cause (80 %) of iatrogenic bilateral vocal fold immobility and 30 % of all bilateral immobility [1].

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Dysphonia is commonly associated with thyroid disease and after thyroid surgery, and this is not always associated with injury to the recurrent laryngeal nerve (RLN) or superior laryngeal nerves (SLN). The location of the recurrent laryngeal nerves adjacent to the thyroid gland leads to the risk of RLN injury either from thyroid disease or during thyroid surgery. In addition, there have been shown to be voice abnormalities in many patients following thyroid surgery even when the RLN and SLN nerves have been preserved. Voice disturbances may be identified in up to 80 % of patients following thyroid surgery [2], with some of this risk being related to commonly occurring dysphonia after general anesthesia or in some cases due to changes in laryngeal structure mobility following the anterior neck surgery and subsequent healing or scarring.

In addition, approximately 1 in 10 patients experience temporary laryngeal nerve injury after surgery and more permanent nerve injury (either paralysis or paresis) occurring in up to 4 % of patients [3]. There has been a gradual increase in the percentage of total thyroidectomy cases; in comparison topartial thyroidectomy, there is an increased overall risk to the laryngeal nerves [3]. Although temporary hoarseness is not uncommon in any surgery that involves general anesthesia, the potential for laryngeal nerve injury in thyroid surgery mandates greater concern when hoarseness occurs after this type of procedure [4].

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Table 9.1 Etiology of unilateral vocal fold immobility 1985–2005 [1]

	1985–1995		1996–2005		1985–2005	
	n	%	*n*	%	*n*	%
Surgery	67	23.9	168	46.3	235	36.5
Thyroid	23	8.2	57	15.7	80	12.4
Nonthyroid	44	15.7	111	30.6	155	24.1
Malignancy	69	24.7	48	13.5	118	18.4
Lung	55	19.6	24	6.6	79	12.3
Metastatic	4	1.4	12	3.3	16	2.5
Thyroid	3	1.1	8	2.2	11	1.7
Esophageal	7	2.5	2	0.6	9	1.4
Other	0	0	3	0.8	3	0.5
Idiopathic	55	19.6	64	17.6	119	18.5
Trauma	31	11.1	8	2.2	39	6.1
Intubation	21	7.5	16	4.4	37	5.8
CNS	22	7.9	11	3.0	33	5.1
Infectious			13	3.6	13	2.0
Inflammation			7	1.9	7	1.1
Radiation			3	0.8	3	0.5
Stenosis			3	0.8	3	0.5
Aortic aneurysm			2	0.6	2	0.3
Other			19	5.2	19	3.0
Total	280		363		643	

Table 9.2 Etiology of bilateral vocal fold immobility [1]

	1985–1995		1996–2005		1985–2005	
	n	%	*n*	%	*n*	%
Surgery	30	25.7	40	55.6	70	37.0
Thyroid	21	18	35	48.6	56	26.9
Nonthyroid	9	7.7	5	6.9	14	7.4
Malignancy	20	17	7	9.7	27	14.3
Lung	6	5.1	3	4.2	9	4.8
Metastatic	4	3.4	2	2.8	6	3.2
Thyroid				0.0	0	0.0
Esophageal	10	8.5	1	1.4	11	5.8
Other			1	1.4	1	0.5
Intubation	18	25.4	7	9.7	25	13.2
Idiopathic	15	12.8	6	8.3	21	11.1
CNS/Neuropathy	15	12.8	5	6.9	20	10.6
Trauma	13	11.1	1	1.4	13	7.4
RA/Inflammation	4	4.3	1	1.4	5	2.6
Radiation	2	1.7	1	1.4	3	1.6
Stenosis			2	2.8	2	1.1
Infectious			1	1.4	1	0.5
Other			1	1.4	1	0.5
Total	117		72		189	

CNS central nervous system, *RA* Rheumatoid Arthritis

The other nerves of major interest, and frequently less directly addressed during thyroid surgery, are the bilateral superior laryngeal nerves (SLN), injury to which can impair the ability to change pitch and reduce voice projection. Another less common surgical cause for post-thyroidectomy voice change is cervical strap muscle injury [3, 5]. General anesthesia can result in a number of potential problems with voice including laryngeal irritation, edema, or other injuries from airway management, such as ulceration or vocal fold granulomas.

Impact of Vocal Fold Paralysis on Voice and Swallowing Function

The obvious result of vocal fold paralysis is loss of voice. The position of the vocal fold is important to the quality of voice, with vocal folds in the lateralized position resulting in worse voice than those in a more medial position. This position is influenced by a number of factors, but most importantly may be the status of the SLN, since combined RLN and SLN paralysis will usually result in a more lateralized position of the vocal fold with greater impact on voice or swallowing. The SLNs are less directly addressed during thyroid surgery although dissection can result in injury, and either unilateral or bilateral superior laryngeal nerve injury can impair the ability to change pitch and reduce voice projection [6]. The larynx plays other important roles unrelated to voice. One of them is to attain tight closure which is necessary to Valsalva which is necessary for heavy lifting and can reduce strength and may have an impact on exercise tolerance. It can also result in a perception of shortness of breath The last important function of the larynx is the control of swallowing. Tight vocal fold closure is essential to normal swallowing and prevention of aspiration. The more lateral the position of the vocal folds the greater the impact on voice, Valsalva, and swallowing.

Recently, multidisciplinary guidelines, "Clinical practice guideline: Improving voice outcomes after thyroid surgery, have been developed to address voice outcomes in relationship to thyroid surgery" [3]. This focused on how to address the patient with disordered voice before and after thyroid surgery. Their recommendations are noted in Table 9.3 [3]. The important principles are to assess patients before and after thyroid surgery, and if there is any concern related to the voice, then appropriate assessment and direct visualization of the larynx are indicated [3]. Injury to the laryngeal nerves is possible with any anterior neck surgeries including thyroid, anterior cervical spine fusion, or carotid endarterectomy or surgery in the upper chest or mediastinum [1]. In many of these cases, the patient may have a relatively normal voice. Surgery in such patients dramatically increases the risk of bilateral vocal fold paralysis which is much more complex to manage than a unilateral paralysis. Laryngeal evaluation is therefore recommended in any patient who has had prior anterior neck surgery if thyroid surgery is being planned [3]. This is a notable area of controversy in that some feel that every patient should undergo a laryngeal examination prior to thyroid surgery as paresis, and even paralysis of one unilateral RLN can occur with a grossly normal voice. This identification may lead to higher suspicion of a malignancy and may alter the planning and execution of the surgery.

Initial assessment of potential voice problems in patients scheduled for thyroid surgery or in patients who have recently had thyroid surgery can be through a number of different methods. The surgeon or endocrinologist could ask the patient and family if they perceived a change in voice, a subjective assessment of dysphonia could be made by any team member, or a validated quality of life instrument like the Voice Handicap Index (VHI) [7] could be administered. If any concern is raised, then an evaluation by an otolaryngologist is recommended [3].

There has been a recent report looking at the impact of unilateral or bilateral vocal fold paralysis following thyroid surgery. 76 patients who sustained either unilateral or bilateral vocal fold paralysis were compared to 238 patients who did not have injury during thyroid surgery. The two groups are matched to age, sex, race, and type of procedure. The authors found that, "Patients who

Table 9.3 Clinical practice guideline: Improving voice outcomes after thyroid surgery [3]

1.	Document assessment of the patient's voice once a decision has been made to proceed with thyroid surgery
2.	Examine vocal fold mobility, or refer the patient to a clinician who can examine vocal fold mobility, if the patient's voice is impaired and a decision has been made to proceed with thyroid surgery
3.	Examine vocal fold mobility, or refer the patient to a clinician who can examine vocal fold mobility, once a decision has been made to proceed with thyroid surgery if the patient's voice is normal and the patient has (a) thyroid cancer with suspected extrathyroidal extension, or (b) prior neck surgery that increases the risk of laryngeal nerve injury (carotid endarterectomy, anterior approach to the cervical spine, cervical esophagectomy, and prior thyroid or parathyroid surgery), or (c) both
4.	Educate the patient about the potential impact of thyroid surgery on voice once a decision has been made to proceed with thyroid surgery
5.	Inform the anesthesiologist of the results of abnormal preoperative laryngeal assessment in patients who have had laryngoscopy prior to thyroid surgery
6.	Take steps to preserve the external branch of the superior laryngeal nerve(s) when performing thyroid surgery
7.	Document whether there has been a change in voice between 2 weeks and 2 months following thyroid surgery
8.	Examine vocal fold mobility or refer the patient for examination of vocal fold mobility in patients with a change in voice following thyroid surgery
9.	Refer a patient to an otolaryngologist when abnormal vocal fold mobility is identified after thyroid surgery
10.	Counsel patients with voice change or abnormal vocal fold mobility after thyroid surgery on options for voice rehabilitation

suffer a unilateral or bilateral VFP after undergoing thyroidectomy experience significantly more morbidity than similar patients who do not have VFP after thyroidectomy. The VFP patients incurred significantly more charges for health care in the first 90 days after surgery. The likelihood of experiencing VFP was not related to malignancy, BMI, or thyroid gland weight in this series." [8]

Technical Caveats to Avoid Nerve Injury During Thyroidectomy

The avoidance of nerve injury in thyroidectomy is centered on injury prevention measures that begin not during surgery but rather at the time of the initial evaluation of the patient. This evaluation is coupled with intraoperative and postoperative management decisions that optimize patient outcome. A detailed history, review of pathology, outside surgical records if applicable, and review of surgical indications with the patient and family are necessary to assess risk. For example, patients with a history of Hashimoto's thyroiditis or prior thyroid or parathyroid surgery could certainly pose a greater intraoperative risk to the recurrent laryngeal nerve (RLN), superior laryngeal nerve (SLN), and even the vagus nerve depending on the extent of central and lateral neck disease that may need to be addressed during the operation.

This history is complemented with both preoperative physical exam and careful review of radiologic imaging. The physical exam should not only include careful palpation of the thyroid, central and lateral neck, but also attention should be paid to the vocal exam with a recommendation to strongly consider viewing the vocal folds by indirect laryngoscopy or flexible laryngoscopy for every patient in which surgery is contemplated. The voice could be remarkably normal to perception even in the face of a nerve compromise resulting in vocal fold immobility. This may result in alterations in surgical planning and preparation including the intensification of imaging studies for evaluation. Ultrasound is recommended by the American Thyroid Association Guidelines prior to surgery [9] and should be reviewed prior to surgery, particularly if it is not performed by the operating surgeon during the

initial evaluation. In addition, cross-sectional imaging provided by CT scan or other imaging modalities should be considered contingent upon the specific situation. The position of a large substernal goiter in the posterior mediastinum or extensive central or lateral neck disease can provide valuable pretreatment probability concerns for nerve risk. Invaluable feedback from a multidisciplinary thyroid tumor board can further enhance the pretreatment preparation.

After the preoperative preparation has been properly performed, the experience of the surgeon is of great importance to avoid nerve injury intraoperatively. Studies have shown that the incidence of thyroidectomy complications including nerve injury is directly proportional to the extent of surgery and inversely proportional to the surgeon's experience [10, 11]. Experienced surgeons with low nerve complication rates are guided by principles to which they adhere with great discipline. Meticulous hemostasis throughout the surgical procedure cannot be overemphasized. It affords the surgeon with a clear view, often aided with loupe magnification, of the operative field to identify critical anatomic landmarks that lead to the identification of the recurrent laryngeal nerve. Recurrent laryngeal nerve visualization is currently considered the gold standard for nerve preservation [12]. Hemostasis is of importance in not only identifying the nerve but also in preventing injury to the nerve from injudicious electrocautery heat in anatomic proximity to the nerve that could result in permanent nerve injury despite an intact nerve. Precise bipolar rather than monopolar cauterization, suture tying, or clipping of vessels with attention paid toward not incorporating portions of the nerve or causing crush injury have been successful strategies to avoid nerve injury in this manner. In addition, advanced energy devices including the harmonic scalpel and Ligasure have been used as another strategy to achieve this and have received literature support in regard to their effectiveness [13, 14].

The precise handling of tissue around the nerve to prevent stretch or traction injury on the nerve is of utmost importance. There is limited data in the literature to suggest that approximately 10 % of nerves that are traumatized are visually identified and appreciated as injured by the surgeon [15]. This places further emphasis on the importance of tissue handling and management of hemostasis. Nerve transection, which would generally be appreciated by surgeons who routinely identify the nerve, the standard for nerve protection, may not be as common of a contemporary reason for nerve injury.

Although the routine use of neural monitoring in thyroid surgery is controversial, there are clinicians who are proponents of its routine use to benefit patients. A commonly used strategy is an electromyographic (EMG) system utilizing a specialized endotracheal tube with electrodes to monitor activated laryngeal musculature secondary to stimuli including pressure, heat, traction, or intentional stimulation with a probe [16]. The application of intraoperative neural monitoring (IONM) can assist in neural mapping using the neural monitor probe at 2 mA to electrically map the course of the nerve in the paratracheal region. It can be used to provide insight into pathologic states of the RLN, particularly with invasive cancers. Furthermore, it can provide neural function prognostication, which is of value when a surgeon is considering the staging of a procedure to prevent a possible airway compromise if both nerves were either temporarily or permanently weakened [12]. Excellent evidence exists that final evoked potential amplitudes on intraoperative electromyography of the recurrent laryngeal nerve correlates with immediate postoperative vocal fold function after thyroid surgery [17]. Finally, preliminary studies are exploring the dynamic assessment of the nerve through continuous vagal monitoring. This could be advantageous to alert the physician regarding EMG changes that may herald an impending nerve injury and allow for modification of surgical maneuvers to reverse the situation [18, 19].

Contemporary Guidelines by the American Academy of Otolaryngology and Head Neck

Surgery have proposed IONM as a consideration for patients specifically for bilateral thyroid sur-

gery to avoid bilateral vocal cord paralysis through prognostication of postoperative vocal cord function, revision thyroid surgery, and in the setting of an existing RLN paralysis for the aforementioned rationale [3, 12].

There is no substitute for identifying the nerve to reduce inadvertent nerve injury rates [20]. Experienced surgeons are adept at locating the nerve at various locations along its course. Some would advocate against dissecting the nerve along its entire course but rather to identify it at key locations and protect it [16]. If a central nodal dissection was to be performed for malignancy concerns, the course of the nerve demands an extensive dissection. This has fortunately not resulted in higher levels of nerve injury when reviewed in meta-analysis but does represent the experience of high-volume surgeons and institutions that may have resulted in biased results regarding nerve injury when compared to most practitioners [21]. In regard to the course of the nerve, the nerve must enter the larynx, and the cricoid cartilage is a very easily palpable landmark. The nerve courses behind the cricothyroid joint. One must be aware of potential extralaryngeal branching of the nerve at this point and protect all branches as the ligament of Berry is divided. The nerve is also found in the trachea-esophageal groove, where it has a variable relationship to the inferior thyroid artery. It is most often deep to the artery, but it can be either superficial or deep to this artery or even branch around it. Finally, the tubercle of Zuckerkandl, which is present in 60–90 % of patients and thought to be a remnant the ultimobranchial body, serves as an important site to locate the nerve. The RLN often will pass posterior and medial to the tubercle [16, 22]. The normal anatomic relationships can be obfuscated by both primary or regional metastatic nodal thyroid cancer and displacement by large goiters or multinodular goiters. An unusual variant of the nerve course that merits attention is a nonrecurrent laryngeal nerve. This is almost exclusively on the right side for patients who do not have situs inversus of their thoracic organs. It could be preoperatively suspected if a patient was found to have an anomalous retro-esophageal subclavian artery causing dysphagia lusoria.

Management of the Severed Nerve Intraoperatively

Although the majority of nerve injuries are not identified intraoperatively, a severed nerve should be repaired when appreciated. The exact mechanism of repair is controversial, and the variability in outcome can often be disappointing. A direct repair can be performed if it is done without tension on the nerve anastomosis using 9–0 nylon suture to re-approximate the epineurium with 3–4 sutures under microscopic assistance. If there is anticipated tension on the nerve anastomosis, the nerve can be transposed on the right around the subclavian artery to gain length. Alternatively, the cricopharyngeus muscle can be opened to increase the effective amount of nerve tissue present (Fig. 9.1a, b). Our own unpublished cadaveric study of 40 fresh frozen nerves has found this length to average 14 mm on the left and 15 mm on the right. [23] Interposition nerve cable grafting could also be done with a variety of donor nerves in the neck to choose from including the ansa cervicalis nerve or cervical plexus branches [24]. Another potential option is to perform an ansa cervicalis nerve to RLN anastomosis as described below for the long-term management of vocal fold paralysis. This has not been studied in comparison to the direct repair method for an acute nerve injury. The low incidence of events would be difficult to power such a study and make it feasible to evaluate. However, the ansa cervicalis nerve to RLN anastomis may theoretically provide a shorter route for nerve regeneration than the route required from the vagus to the RLN. Medialization procedures discussed separately could also be considered. A vocal fold injection with a variety of substances discussed elsewhere in this chapter may be attractive in that it could provide immediate potential improvement in the acute setting

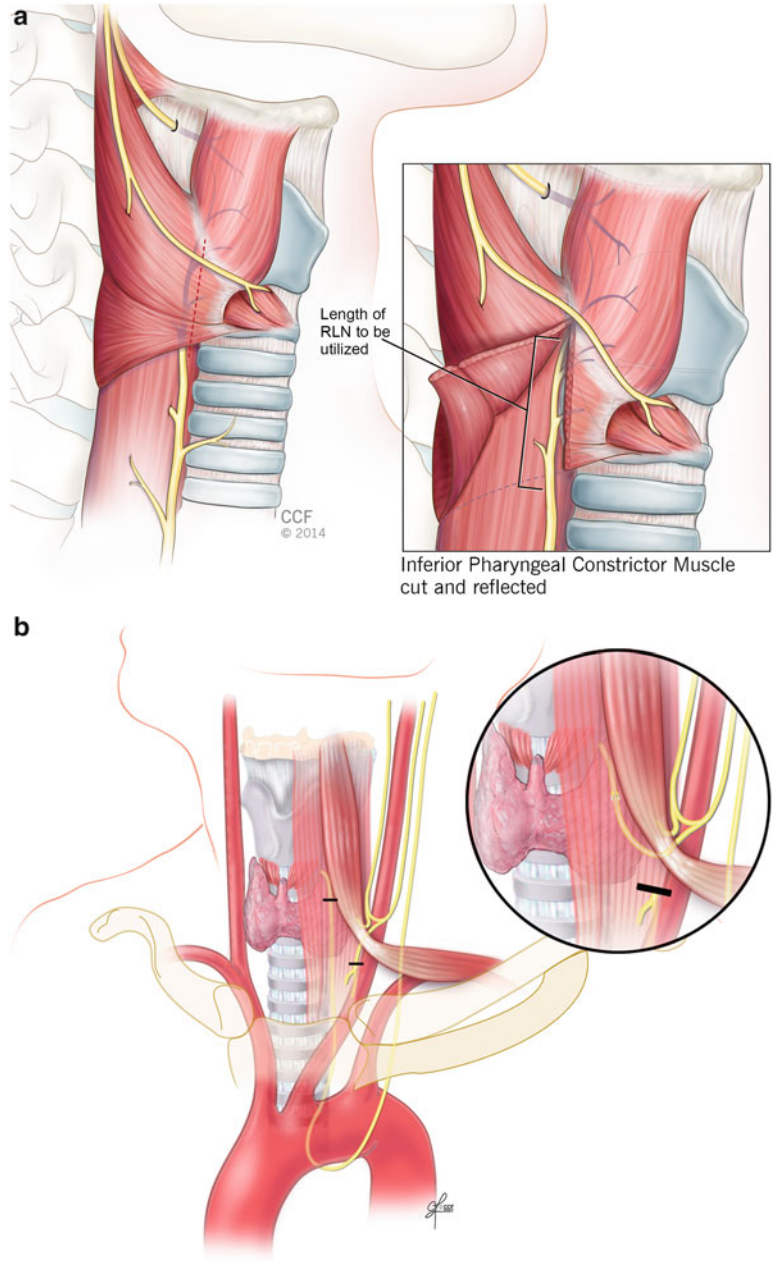

Fig. 9.1 (**a**) Schematic of additional recurrent nerve length available for reinnervation procedures. Reprinted with permission, Cleveland Clinic Center for Medical Art & Photography © 2007–2014. All Rights Reserved. (**b**) Cadaveric anatomic dissection of additional recurrent nerve length available for reinnervation procedures. Reprinted with permission, Cleveland Clinic Center for Medical Art & Photography © 2007–2014. All Rights Reserved

and still allow for future secondary injections, nerve reinnervation procedures, or medialization laryngoplasty procedures. It is certainly important to address candidly and in a timely manner the consequences of a recognized injury with the patient and family so that options for voice reconstitution can be more expediently pursued.

Although great emphasis has always been placed on the RLN, the importance of the external branch of the superior laryngeal nerve (EBSLN) should not be discounted. The external branch of the superior laryngeal nerve innervates the cricothyroid muscle to tense and lengthen the vocal folds. This affords patients the ability to

achieve a high pitch in the voice, which can be very important for professional voice users, especially singers. Injury to this nerve is often unrecognized due to variability in vocal changes postoperatively and difficulty in readily identifying physical examination findings consistent with its injury. In contrast to the routine identification of the recurrent laryngeal nerve for optimizing vocal outcome, the routine identification of the superior laryngeal nerve is very controversial among even experienced thyroid surgeons. Some clinicians advocate protecting the nerve without insisting on the direct visualization of the nerve. They argue that the routine identification of the nerve places it at a higher risk for injury. En mass ligation of the superior pole vessels is discouraged. Instead the cricothyroid space is opened to allow the superior vessels to be carefully controlled. Patients with a high-riding superior thyroid pole, superior thyroid nodules, or goiters are at greatest risk for injury [16]. The nerve's anatomic variants have been carefully described, and the nerve will have an inferior course and be very susceptible to injury 20 % of the time with the technique of mass ligation of the superior pole vessels. EBSLN types 2a and 2b are the specific variants that will course in close association with the superior pole vessels and/or superior to the gland's surface [16, 25]. The routine monitoring of the SLN is even more controversial than monitoring of the RLN and still a preliminary experience in select centers. A prospective multiple tertiary care center study evaluated intraoperative neural monitoring to assist in EBSLN identification during thyroid surgery, and a novel endotracheal tube did allow for quantifiable EBSLN EMG activity in all cases [26].

Management of Vocal Fold Paralysis Following Thyroid Surgery

The paradigm for management of vocal fold paralysis following thyroid surgery has changed with improvement of methods to medialize the vocal fold, the advent of better injectables, and the general adoption of office-based procedures. In the past, it was not uncommon for people to wait for long periods of time, often up to 1 year, while waiting to see if there would be nerve recovery in cases where VFP was identified but the nerve was preserved following surgery. Recent reports have shown that early treatment is much better than the wait and see approach. There have been a number of studies that have shown that early injection of the unilateral paralyzed vocal fold reduces the likelihood that a permanent procedure such as on open medialization laryngoplasty or innervation procedure would be needed even if nerve function does not return [27, 28]. This may have to do with the ability to return the immobile vocal fold to a medial position, where more normal function can occur, and hyperfunction and aberrant vocal fold motion may be prevented. Because of this, it is common to proceed with an early injection of a resorbable injectable material in order to return the patient to more normal voice and swallowing function while the ultimate motion of the vocal fold had not been definitively determined. This is particularly true in patients who are aspirating early after loss of function. Although this is a reasonable approach and one that we will often take, this early intervention approach has the disadvantage that final treatment may need to be delayed to allow for the injected material to completely resorb prior to implementing the definitive treatment.

Laryngeal EMG is very useful in helping to predict outcome and in aiding in trying to determine the timing of those outcomes. In general, permanent procedures are delayed until the likelihood of recovery becomes very small. An EMG performed between 3 and 6 month is a good time frame. At that time, an EMG that shows no innervation, minimal reinnervation, or some reinnervation with poor recruitment are all such poor long-term prognostic signs that proceeding with permanent procedure is reasonable.

No matter what intervention is recommended, whether it is medical, functional, or surgical, it is very important to obtain reproducible data to compare pre-intervention and post-intervention results. Although there are many tests that can be performed, we always obtain three evaluations: laryngeal stroboscopy, which is recorded in a

reproducible fashion for comparison; maximum phonatory time (MPT); and quality of life assessment with the Voice Handicap Index (VHI) [7]. These allow us to assess vibration, airflow, closure, and patient perception of quality of life impact. The VHI also allows for comparison with other studies. The MPT could also potentially allow for comparison with other studies, although the methods of obtaining these values vary between groups which may limit somewhat direct comparisons. It does give a very good evaluation between preoperative and postoperative results in an individual patient and allows for a good measure of the effectiveness of medialization in a patient who is having a procedure under local anesthesia in the operating room or with office-based injection procedures.

Vocal Fold Injection

Vocal fold injection has been a mainstay for medializing the paralyzed vocal fold dating back to the early 1900s when paraffin was injected into the vocal folds. Complications were high, and it was not until the 1970s when a viable alternative was reported with the advent of injecting Teflon® for vocal fold medialization [29]. Unfortunately, a number of patients developed a granulomatous reaction that effected long-term outcomes. More recently, a number of other injection options have been developed for vocal fold injection. Some of these are preferably done either in the office or operating room. There is general agreement that the ideal material for injection laryngoplasty should be biocompatible, easy to inject with minimal preparation, and possess a residence time that offers the patient a reasonable period of benefit prior to reabsorption [30, 31].

There are a number of injectable materials that are now commercially available that meet the above criteria. Some of these are easier to use in the office than others. Gelfoam® has been a mainstay of short-term injection material for many years. It gives a good overall assessment of the success expected with more permanent injection or with either other short acting or longer acting substances or formal medialization. The very short time of effectiveness (<6 weeks), the difficulty in preparation, and the development of easier and longer acting injectables have limited its use. Cimtra® is a Micronized Dermis (MD) which is a product from skin that is relatively easy to use either in the office or in the operating room. The product does require some preparation prior to use, but in practices where it is routinely used this process is relatively quick. Good results with Cimetra® injections both short and long term have been reported [32]. Hydroxylapatite crystals are commercially available for injection under the trade name Radiesse®. A number of studies have reported good success and some sustained effect [33]. The product is expected to last for 6–12 months, but there is significant variability. It also has been shown to have some undesired tracking into areas of the larynx where it was not desired. The pliability of Radiesse® is much stiffer than that of the true vocal fold, and superficial injection can lead to stiffness, which can dramatically affect the quality of the voice. Injection should be lateral as possible to allow the vocal fold to be pushed medially but not result in stiffness. These limitations have led to a number of surgeons to inject Radiesse® in the confines of the operating room where there is more control rather than in the clinic where the movement of the vocal fold may lead to injection in an unfavorable location. Another disadvantage of Radiesse® is that the product can last up to 2 years, which may delay the timing of a permanent procedure if vocal fold movement does not return and if the voice remains poor. The carrier of the hydroxylapatite has also become available as a short-acting injectable (around 6 weeks) under the name Radiesse® gel.

Hyaluronic acid (HA) is a naturally occurring polysaccharide in the extra cellular matrix of human cells [34, 35]. It has also been identified within the vocal fold lamina propria [34]. There are multiple forms of HA available in an injectable form. Restylane® (Q-Med AB, Uppsala, Sweden) is a commercially available form of cross-linked HA. It is clinically used as a dermal filler in plastic and cosmetic procedures and is used by otolaryngologists in an off-label fashion for injection medialization. There are a number of advantages

to using hyaluronic acid for vocal fold injection. It has similar weight and vibratory characteristics to the native vocal fold, and hyaluronic acid does exist in vivo in the normal vocal fold. Early after injection, hyaluronic acid remodels so that even if there is poor placement it will redistribute to allow for a smoother vocal fold edge. It is very easy to use in the office and lasts for around 3 months which gives an adequate length of time to allow for better assessment of potential outcomes or the need for additional therapy. Very good results have been reported [36]. For these multiple reasons, hyaluronic acid (Restylane®) has become our temporary treatment of choice.

Autologous fat can be harvested from the patient and then injected into the vocal fold. Fat has a number of theoretical advantages over the commercially available injectables. Fat has viscoelastic properties very similar to that of the normal vocal fold so that vibration and pliability are retained without stiffness. It is readily available as only small amounts are needed to be harvested. There is also some evidence that there are stem cells within the fat which can integrate into the normal vocal fold tissue. One down side is that the long-term results are unpredictable as variable amounts of fat are resorbed by the body, so the fat has to be over-injected and the results are not predictable. It also is not very helpful in moving a lateralized vocal fold. In most cases, it needs to be injected in the OR, although some use it in the office. Its best use is in paralysis with a small defect where injection can result in permanent benefit. There are multiple controversies related to fat harvest and injection and these include how to harvest and process the fat as well as the best way to inject it.

There is notable controversy related to not only the timing of intervention but which injectable should be used. It can be argued that the previous watch and wait approach is no longer state of the art and that an early intervention should be provided. If the doctor managing the patient is not capable of performing an injection, should the patient be referred to one who can? In addition, given the need to wait long periods of time for resorption of some products, and that a determination can be made regarding prognosis earlier with EMG assessment, should shorter acting injectables be primarily used in cases where recovery is possible? Finally, it is clear that the cost of office injections is dramatically lower than in the operating room while the outcomes are comparable with most injectable products, should surgeons who are unable to perform office injections not consider referral to one that is able to and is available? These controversies are currently being sorted out but the scales are tipping towards: (1) Early injection wherever possible, (2) earlier EMG assessment to help assess long-term prognosis (typically between 3–6 months), (3) short-term injectables unless it is clear that there may be a long time to recovery or no recovery is likely, (4) office injection rather than operating room injections where possible.

Long-Term Management of Vocal Fold Paralysis

Medialization Laryngoplasty and Arytenoid Adduction

Although there is notable debate over the best method for long-term management of vocal fold paralysis, static repositioning of the vocal fold to the midline to allow for appropriate contact from the opposite vocal fold has become the primary method of treatment. This can be performed in 2 ways: placement of a vocal prosthesis (medialization laryngoplasty) or rotating the arytenoid (arytenoid adduction). The decision to perform one of these procedures is also controversial. Many believe that a lateralized vocal fold requires a rotation of the arytenoid, although in most cases of unilateral vocal fold paralysis, the vocal fold is in a position where medialization alone can lead to very good voice outcomes.

Medialization laryngoplasty has been routinely performed since first described by Isshiki [37]. There have been multiple techniques described as well multiple materials used to medialize the vocal fold. Despite the magnitude of the papers that describe these procedures, few show any objective results after medialization. Our results following medialization with silastic in 78 patients were recently reported. Pretreatment mean VHI (total score) was 67 for the entire

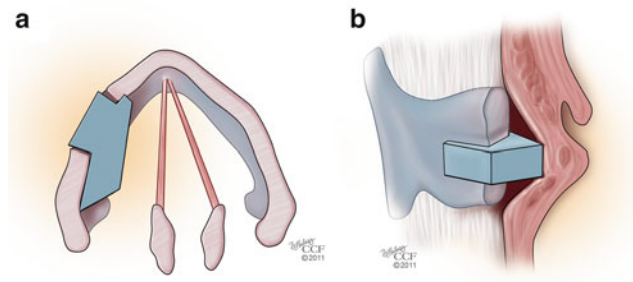

Fig. 9.2 Medialization laryngoplasty with Silastic from superior (**a**) and lateral (**b**) view. Reprinted with permission, Cleveland Clinic Center for Medical Art & Photography © 2007–2014. All Rights Reserved

cohort. Postoperative VHI score was significantly lower both in short-term (3–8 weeks) follow-up, mean score 27, and in long-term follow-up (9–12 months), mean score 22. MPT was significantly improved from 8.3 pretreatment to 22.6 at short-term follow-up and to 24.2 long-term follow-up. Figure 9.2 of note, patient with lateralized vocal folds or those with a high vagal lesion, where many suggest that an arytenoid rotation is needed, showed similar results to the entire group, and better than reported cases of combined MLS and arytenoid adduction. These results clearly validate that this technique is effective in improving voice and voice related quality of life. Of interest, these scores would seem to gradually improve over time after medialization. Although long-term follow-up was only available in a subset of patients, we have seen gradual improvement of both VHI and MPT scores over the first year postoperatively [38].

Although there are a number of materials that are described to medialize the vocal folds, we prefer to use carved silastic (solid silicone). The reasons for this are multiple. Carving a prosthesis for each patient allows for an individualization of the results based on the size of the thyroid cartilage and larynx and the angle of the anterior thyroid cartilage. If the prosthesis is too large or too small, it can be modified during the operation. If the window is slightly in the wrong position, there is the ability to modify the prosthesis to allow the implanted portion to align with the vocal fold but still fit the window. Finally, the position of the implant at the time of surgery will be maintained after surgery as it is held in place by the inner perichondrium and muscle medially and the thyroid cartilage laterally, and it cannot rotate based on the way it is wedged in the window. One of the disadvantages of carved silastic is that it truly takes significant experience in carving the prosthesis to be able to judge location and size. If done properly, we have found that it can often push the vocal process medial so that over time we have performed less arytenoid adduction procedures.

Although there are other implanted materials and devices, there are some disadvantages to silastic. Gortex is easier to use and place and has the similar advantages as silastic as it can be adjusted based on the observation of the larynx and the quality of voice. One major disadvantage of gortex is that once the tunnel has been created, the position of the gortex is determined. If it is too large or too high or low, it is hard to hold the gortex in the preferred position. In addition, we have found that the results at surgery decrease slightly over time, likely because of compression of the gortex with use. It may be necessary to slightly overcorrect the implantation to allow for this gradual change. The prefabricated implants have multiple disadvantages. They are expensive and size specific, so they are difficult to modify. If the size is not correct, then an additional prosthesis would need to be used, adding additional cost. Even with a few sizes, the implant might not be correct for some patients. For all of these reasons, we prefer silastic medialization. To these ends and to allow for less experienced surgeons to perform the procedure, we have developed a formula to allow ease of carving based on

preoperative CT scans [39]. Since many thyroid surgery patients have had a CT obtained, creating a templated prosthesis should be possible in those patients and results may be more predictable.

Reinnervation

Laryngeal reinnervation refers to any method that seeks to reconstitute neural pathways to the vocal fold. The methods include nerve–muscle pedicle, muscle–nerve–muscle pedicle, and donor nerve–recurrent nerve (RLN) anastomosis [40–42]. Specific nerve strategies for reinnervation include primary RLN anastomosis (primary RLN), ansa cervicalis-to-RLN neurorraphy (ansa-RLN), ansa cervicalis-to-thyroarytenoid neural implantation (implantation), ansa cervicalis-to-thyroarytenoid neuromuscular pedicle (NMP), hypoglossal-to-RLN neurorraphy (hypoglossal-RLN), phrenic nerve-to-RLN (phrenic-RLN), and cricothyroid muscle–nerve–muscle neurotization (CT MNM) [43]. These aforementioned strategies take advantage of the anatomic proximity of the other functioning nerves to improve tone and/or mobility of the paralyzed side without incurring tremendous nerve donor site morbidity [44]. Although reinnnervation procedures can lead to good results in some patients, unlike medialization laryngoplasty, the results are unpredictable and there is a delay between surgery and the final outcome. In addition, success rates are reduced in older patients and if performed after a delay of a few years.The approaches have been further divided into selective and unselective reinnervation.

Selective reinnervation has focused on reestablishing functional mobility of the vocal folds to alleviate synkenesis by targeting reinnervation to one or more muscles. Selective innervation will target different muscles, laryngeal adductor, and abductor muscles, in the same setting. For example, there has been the development of techniques with promising results both in animal models and in humans for those devastated by bilateral vocal cord paralysis, which could occur during thyroidectomy. The technique reinnervates the posterior cricoarytenoid (PCA) muscle with one right upper phrenic nerve root to trigger vocal fold abduction during the respiratory cycle. The adductors are reinnervated with thyrohyoid branches of the hypoglossal nerve [45, 46].

In contrast, unselective reinnervation, most commonly performed for unilateral vocal fold paralysis, aims to provide tone and bulk to the laryngeal muscle to improve closure of the glottis gap and enhance patient perceptual vocal evaluation and quality of life [40]. This approach has been studied more extensively as it captures a much larger cohort of patients afflicted with a unilateral vocal cord paralysis. A diagrammatic depiction of this reinnervation is provided in Fig. 9.1. Proponents of reinnervation cite excellent long-term results and still enjoy the other options for voice reconstitution should the reinnervation fail. A unique advantage of the approach is that it restores vocal tone without affecting mucosal wave properties [40]. Injection laryngoplasty, often done concomitantly to provide an immediate benefit while the nerve reinnervation reaches its optimal outcome at 4–6 months, can be performed, and laryngeal framework surgery including medialization thyroplasty can also still be done without having compromised their effectiveness as options.

Failure to reestablish functional mobility of the vocal cord after nonselective reinnervation has been attributed to laryngeal synkenesis, the aberrant regeneration of abductor, and adductor motor axons resulting in mass movement. Spontaneous reinnervation has been shown both in humans and in animal studies by electromyography and histology when no surgical innervation is performed [47]. In a systematic review of laryngeal reinnervation techniques, the most common reinnervation technique was the ansa cervicalis-to-recurrent laryngeal nerve anastomosis (Fig. 9.3). It was most commonly performed after thyroidectomy, 43.5 % [43]. In the review, all the studied reinnervation techniques provided improvement in symptoms to varying degrees based on perceptual, visual, electromyographic, or acoustic outcomes. The second-most studied method was primary RLN anastomosis, and this was solely associated with thyroid disease and/or surgery. A meta-analysis does not exist to

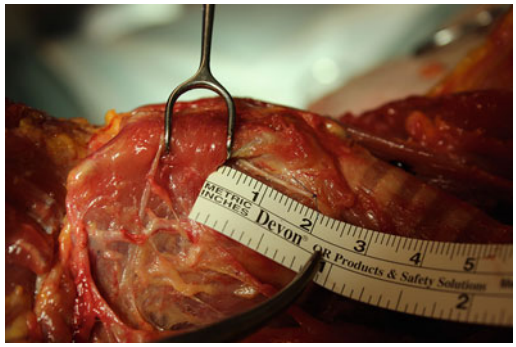

Fig. 9.3 Left ansa cervicalis nerve to left recurrent laryngeal nerve anastomosis. Used with permission of RR Lorenz, MD

further clarify results and was unable to be performed due to study design heterogeneity, population characteristics, intervention, time, and method of outcome assessment. Deficiencies do exist in multiple studies concerning data acquisition purposes, follow-up, sampling methods, and accounts of missing data [43]. Our own single institution series at the Cleveland Clinic Foundation Head and Neck Institute evaluated a total of 46 patients with unilateral vocal fold paralysis. Stroboscopic analysis and perceptual vocal evaluation were performed in a blinded fashion in 21 patients. Severity, roughness, breathiness, and strain all improved significantly over time. In addition, glottis closure, vocal fold edge, and supraglottic effort all significantly improved after the operation. In fact, of 38 patients with at least 3 months follow-up, all but 1 demonstrated evidence of reinnervation [40]. A multidisciplinary approach to engage the patient and family in these complex rehabilitation efforts including reinnervation is ideal.

There is, therefore, evidence of the potential success of improving voice function with reinnervation procedures. There are a number of controversial issues as to whether this is the best approach. With the predictability of static medialization procedures and the relatively lower predictability of the reinnervation procedures, should these be offered as a standard option in all patients? The prior theories that failure of reinnervation can lead to atrophy and therefore gradual loss of the success of the medialization procedures have been largely discredited since innervation can occur from other nerves innervating the larynx and that long-term results of medialization can be sustained [48]. Should a static procedure be performed with either medialization or injection with patients undergoing reinnervation? Should reinnervation procedures be only offered to the patients with the best chance of success: younger patients with relatively recent nerve injury who have only a recurrent laryngeal nerve injury? As reinnervation research continues and the physiology of the success of various reinnervation techniques are clarified, the role of reinnervation will be further elucidated. At this time, due to the predictability of the static medialization procedures, most otolaryngologists rely on injection or medialization as their primary treatments.

Management of Bilateral Vocal Fold Paralysis

Bilateral vocal fold paralysis following thyroid surgery presents a number of different issues than unilateral paralysis. Following surgery, at the time of extubation, there may be stridor which may result in re-intubation or even tracheotomy. High dose steroids may reduce the edema following intubation that may lead to the emergency airway management. Avoidance of tracheotomy may help to facilitate treatment in the future. In addition, many patients who initially start out very breathy when the vocal folds are in a lateralized position will gradually notice voice improvement as the vocal folds become more close together. Why this occurs may be due to synkenesis or the unopposed action of bilateral cricothyroid muscle contraction gradually pulling the vocal folds together. Over time this may progress to result in gradually worsening airway obstruction that may require intervention.

The focus of surgical therapy has predominantly been directed at vocal fold lateralization, although there is growing interest in reinnervation [46] and laryngeal pacing [49]. There are a number of reliable lateralization techniques [50–55] but there are wide variations in success

rates, and postoperative sequelae such as granulomas may occur. In addition, many traditional techniques are best performed with a tracheostomy in place. A lateralization procedure that removes the vocal process and portion of the body of the arytenoids with preservation of the medial mucosa and with/without an external stitch lateralization is described [53]. This procedure has a 90 % or better success rate with minimal risk of granulation formation and can usually be performed without a tracheostomy. A consideration between the opposing balance between quality voice and quality airway is needed in all procedures.

Conclusion

There are a number of controversies related to vocal fold paralysis in relationship to thyroid surgery. These include aspects related to the evaluation and primary surgery including whether or not to do a laryngeal assessment in all patients, is interoperative monitoring indicated, and should the RLN always be identified. Similar controversies apply to patients who have had a vocal fold paralysis develop with surgery. Should the nerve be explored and should an immediate anastomosis be performed? How soon after the injury should a procedure be performed and what is the best option for treatment for the individual patient? Most of these have good evidence to support one choice or another but in some cases there is more than one appropriate decision.

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Part II

Cancer Topics

Optimal Treatment for Papillary Microcarcinoma

10

Mark D. Pace and R. Michael Tuttle

Epidemiology

Papillary Thyroid Microcarcinoma: A Small Cancer with "Epidemic" Proportions

The incidence of well-differentiated thyroid cancer (WDTC) is increasing worldwide, having nearly tripled from 3.5 per 100,000 to 11.4 per 100,000 in just under four decades in the United States [1–3]. Similar trends have been reported across Europe, Canada, South America, Asia, and Australia [4, 5]. This increase is virtually entirely attributable to a rise in the diagnosis of papillary thyroid cancer (PTC), with no significant change in the frequencies of follicular, medullary, and anaplastic cancers during this period [2, 3]. Moreover, PTC 10 mm or smaller in maximal dimension, termed papillary thyroid microcarcinoma (PTMC), made up just under half (49 %) of these new diagnoses [1, 2]. In fact, the incidence of PTMC in the United States increased from 1.5 per 100,000 in 1968 to ~3.5 per 100,000 in 2002. Whether this rise represents a true increase in the disease or an apparent increase caused by improved diagnostic scrutiny exposing an underlying population of subclinical thyroid cancer is a matter of contention.

A number of non-etiologic factors have been suggested as potential contributors to this phenomenon. Enhanced diagnostic scrutiny due to the widespread implementation of sensitive diagnostic techniques has made it possible to detect a subclinical subset of disease. Prior to the introduction of ultrasonography (US) of the thyroid, clinicians relied entirely upon physical examination, a technique that detects only around 40 % of nodules larger than 1.5 cm in size [2]. US, which came into widespread use in the 1980s, can detect nodules as small as 3.0 mm in size [6]. The implementation of US-guided fine-needle aspiration biopsy (FNAB) in the 1990s enabled the sampling of these very small thyroid nodules [4]. In addition, the development of highly sensitive imaging modalities for the investigation of unrelated conditions, such as carotid Doppler US, magnetic resonance imaging (MRI), and positron emission tomography (PET), led to increased incidental detection of asymptomatic PTC. This is consistent with the observation that PTMC is more prevalent in affluent populations with ready access to healthcare and consequent over-investigation.

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Shifts in clinical practice have also contributed to the increase in thyroid cancer diagnosis. For example, more extensive surgical resection for the treatment of multinodular goiter has resulted in a greater volume of thyroid tissue for histopathological examination, facilitating the detection of occult PTC [4]. Some investigators also cite changes in histological criteria introduced by the World Health Organization in 1988. However, this would have been expected to cause an initial surge in diagnoses that would have then resolved. But, despite no further changes to the diagnostic criteria, the trend continues [1, 2, 4].

If this phenomenon were indeed purely the result of enhanced diagnosis, only an increase in small, early stage tumors with a subsequent decrease in larger, more advanced tumors would be expected. Although small PTCs comprise the majority of the diagnostic rise in PTC, an increase in frequency across all tumor sizes and stages has been observed [1, 7]. Consequently, improved diagnosis is not the sole answer. This view is further supported by Londero et al. in their analysis of the changing thyroid carcinoma incidence in the Danish population, in which the authors found that the proportion of thyroid cancer diagnoses accounted for by tumors <20 mm had remained unchanged between 1996 and 2008 [8]. Moreover, 42.8 % of the increase was attributable to tumors >20 mm, and no corresponding change in the use of diagnostic US and FNA biopsy had occurred during this period [8].

A number of potential etiologic factors have also been proposed to explain a true rather than apparent rise in thyroid cancer incidence. During this period, there has been a corresponding increase in environmental chemicals known to be associated with elevated levels of thyroid-stimulating hormone (TSH) [1]. In addition, there has been greater exposure to diagnostic ionizing radiation, particularly the greater use of computed tomography (CT) scanning, as well as other risk factors, such as increasing body mass index (BMI) [1]. Further investigation into the role of these and other potential etiologic factors is warranted.

Despite the increase in frequency of thyroid cancer, the disease-specific mortality rate between 1975 and 2009 has remained stable at 0.5 deaths per 100,000 [3]. In fact, the overall 5-year disease-specific survival rate for patients with thyroid cancer in the United States is 97.8 % [9]. Though this could be explained by major advances in treatment keeping up with rising incidence, thyroid cancer management has remained essentially unchanged since the 1950s. This paradox is attributed by some authors to a lead time bias and that the increased incidence is not yet reflected in mortality data. An alternative explanation is that the majority of the increase in thyroid cancer is due to the diagnosis of a nonlethal subset of the disease, consistent with the concomitant rise in PTMC. Another counterargument to the existence of a true thyroid cancer "epidemic" is that an increase across the entire histological spectrum of thyroid cancer would have been expected. As previously stated, this has not been the case, with only PTC exhibiting a significant increase.

In truth, the thyroid cancer "epidemic" is likely multifactorial and a culmination of these hypotheses, with the majority of the rise attributable to improved diagnosis of subclinical PTMC and a minor contribution from a true increase in PTC incidence.

Implications of the Papillary Thyroid Microcarcinoma "Epidemic"

According to the National Cancer Institute, the estimated number of new thyroid cancer diagnoses in the United States during 2014 was 62,980 [10]. Given that just under half of these can be expected to be PTMC, this represents approximately 30,000 new cases of PTMC. However, autopsy series estimate the prevalence of PTMC to range between 5.6 % and 35.6 % of the population [6, 7, 11]. This wide variation may be due to environmental and genetic factors between populations and differences in histologic techniques employed. Based on such studies, a conservative estimate of 17 million Americans unknowingly harbors foci of PTMC.

The conventional management paradigm of immediate surgical resection often followed by

radioactive iodine therapy remains the most commonly recommended treatment modality for thyroid cancer. However, in the face of rising thyroid cancer diagnoses that are projected to continue due to the high prevalence of occult PTMC, the medical and financial implications of this treatment model are staggering. This is further compounded by sustained low mortality rates and excellent outcomes for PTMC. In addition, the financial impact of a thyroid cancer diagnosis on the patient should not be underestimated. Recent sobering data from the United States identified thyroid cancer as a leading cause of cancer-related bankruptcy [12]. These factors have recently led to a reexamination of the optimal treatment for PTMC.

Outcomes

Natural History of Papillary Thyroid Microcarcinoma

In contrast to the high prevalence of PTMC in the general population derived from autopsy data, the incidence of clinically apparent PTC is just 0.05–0.1 %. This approximate one thousandfold difference indicates that the vast majority of PTMC does not progress to become clinically significant PTC, and as such, it has been suggested that PTMC should be considered a distinct clinical entity [6]. Observed stability in the size of PTMC undergoing active surveillance further supports this. Autopsy studies have found that PTMC 1–3 mm in size is more prevalent than 3–9 mm tumors, which are in turn more common than PTC 10–15 mm in diameter (50.4 %, 27.3 %, and 3.6 %, respectively), suggesting an arrest in growth occurs as part of the natural history of the disease [7]. This assertion is also consistent with the essentially unchanged disease-specific mortality rate in spite of the increasing incidence of thyroid cancer, almost half of which is comprised of PTMC [6]. A divergent biology between the two conditions is also alluded to by differences in patterns of gender prevalence. While clinically apparent PTC is more common in women than in men by a ratio of 3:1, the same disparity is not observed in autopsy studies for PTMC [3]. These observations have led some authors as well as the National Cancer Institute to propose a renaming of PTMC to "occult papillary tumors," removing the term "carcinoma" to better reflect the natural history of the disease, prevent overtreatment, and reduce undue psychological impact on patients [11]. In fact, some have gone as far as to advocate the reclassification of PTMC as a normal finding [2, 11].

The prognosis of the vast majority of patients with PTMC is excellent. Following surgical resection, the disease-specific mortality rate is <1 %, and rates of locoregional and distant recurrence are reported at 2–6 % and 1–2 %, respectively [13, 14]. Interestingly though, similar outcomes have been reported in prospective trials of active surveillance in patients with cytologically confirmed PTMC [15, 16] (Table 10.1). Therefore these favorable outcomes likely reflect the indolent nature of the disease rather than the impact of treatment. Given the excellent prognosis, the traditional management paradigm of indiscriminate immediate surgical intervention is currently undergoing critical reevaluation.

Table 10.1 Outcomes of patients with papillary thyroid microcarcinoma after initial surgical resection vs. active surveillance

	Initial surgical resection	Active surveillance (5 years)	Active surveillance (10 years)
Disease-specific mortality	<1 %	<1 %	<1 %
Locoregional recurrence	2–6 %	1 %	3–4 %
Distant recurrence	1–2 %	<1 %	<1 %
Tumor enlargement (≥3 mm)	–	6–7 %	8–16 %

Risk Factors for Papillary Thyroid Microcarcinoma Progression

Though the vast majority of PTMC remains indolent, a minority of tumors progress to clinically significant disease. Although clinical and histological risk factors predictive of recurrent disease and negative outcomes are well established in conventional PTC, their significance has not been consistently identified in PTMC. However, in general, in the presence of high-risk features, surgical management is recommended.

(a) *Clinical Features*

1. *Age at Diagnosis*—Patient age at the time of diagnosis is a well-established risk factor for survival in PTC; however, its prognostic value in PTMC is less certain. Though the mean age at diagnosis of PTMC is reported to be between 41.9 and 55.0 years, autopsy series have found the prevalence of PTMC to be the constant in each decade throughout adulthood [7]. In a prospective trial of active surveillance of patients with PTMC, Ito et al. observed that primary tumor growth was more likely to occur in younger patients (<40 years), suggesting that older patients are more suitable candidates for active surveillance [17]. Conversely, one study reported that patients with PTMC complicated by distant metastases had a higher mean age than those without metastases (54 ± 16 years vs. 37.7 ± 12.3 years, respectively) [18].
2. *Gender*—A meta-analysis with a combined pool of 6653 patients diagnosed with PTMC found a female to male predominance (ratio 4.85:1.00) [7]. Interestingly, a similar gender disparity has not been reported in autopsy prevalence studies [7]. This paradoxical observation may be partly explained by differences in patterns of access to healthcare between genders. In addition, screening investigations may be performed more frequently in women due to their predilection for thyroid disease, leading to increased rates of incidental identification of subclinical PTMC. Though male gender has been identified as a negative prognostic factor in PTC, gender was not found to be predictive of reduced disease-specific survival in a retrospective, multivariate analysis of 7818 cases of PTMC treated with surgery with or without RAI therapy [19].
3. *Head and Neck Irradiation*—Distinct patterns of RET oncogene rearrangement and cytology have been described in patients with radiation-induced thyroid carcinoma that are associated worse outcomes [20]. However, the clinical outcomes appear to be very similar in radiation-related thyroid cancer and in sporadic thyroid cancer. Therefore, small thyroid cancers that arise in the setting of previous radiation exposure are not expected to be more likely to progress than sporadic thyroid cancers.
4. *Family History of Thyroid Cancer*—Familial cases of PTMC have been reported with an overall prevalence of 4.5 %, a similar frequency to the 5–10 % of all cases of thyroid carcinoma that are familial [7]. While some authors have observed more aggressive behavior in heritable cases, this has not been substantiated by other studies [21].
5. *Mode of Presentation*—A three-tiered, subclassification system of PTMC has been proposed based on the mode of presentation which may assist in guiding therapy [6]:
   - *Incidental PTMC*—Tumors diagnosed on imaging studies or pathological examination following surgical resection performed for other indications
   - *Latent PTMC*—Tumors incidentally discovered at the time of autopsy following non-thyroid cancer-related death
   - *Occult PTMC*—Primary tumors giving rise to nodal and/or distant metastases

Incidental PTMC generally behaves in a biologically inert fashion similar to the latent group found on autopsy and can therefore be managed conservatively, whereas occult PTMC requires definitive management [6].

(b) *Imaging Characteristics*

US findings including tumor multifocality, evidence of extensive extrathyroidal extension, tumor location, an ill-defined margin, and the presence of microcalcifications have been significantly associated with lateral nodal metastases and may serve as prognostic markers.

1. *Tumor Size*—Larger PTMC (>5 mm or >8 mm) have been found to be more frequently associated lymph node metastases at diagnosis but not with risk of regional nodal recurrence [21]. However, Lee et al. evaluated 2014 patients with PTMC who had been treated with lobectomy or total thyroidectomy together with central neck compartment dissection and found that overall survival and disease-free survival did not differ for tumors ≤5 mm or >5 mm in size [22].
2. *Tumor Location*—Location of the primary tumor is not predictive of pattern of metastasis to either central or lateral compartment lymph nodes [21]. However, PTMC in a subcapsular location on the dorsal surface of the thyroid adjacent to the trachea or recurrent laryngeal nerves may place these vital structures at risk of invasion. In addition, isthmic tumors may result in extrathyroidal extension early in the disease course simply due to a limited capacity for expansion.
3. *Tumor Margin*—An irregular tumor margin has been associated with a peritumoral infiltrative growth pattern.
4. *Extrathyroidal Extension*—Disease extending beyond the thyroid capsule may have an increased risk of locoregional invasion and disease recurrence.
5. *Multifocality*—As is the case in PTC, the incidence of multiple foci of PTMC is relatively high. Iyer et al. observed multifocality in 27.2 % of cases, He et al. reported a frequency of 36.3 % in their surgical series, and Lang et al. found that 46 % of PTMC was multicentric [23–25]. Multifocality has been associated with higher rates of locoregional recurrence and nodal metastases, but whether this results in clinically overt disease is contentious.

(c) *Cytological Features*

1. *Higher-Risk Cytological Subtypes*—Less common variants of PTC with established, more aggressive potential have been reported in PTMC. Tall cell and oncocytic variants account for 0.8 % of PTMC, while sclerosing variant is seen in 5.0–11.7 % of cases [7].
2. *High-Grade Cytological Features*—Sugitani et al. showed an increased Ki-67 proliferation index and immunohistological positivity for transforming growth factor β3 predict poor prognosis for disease-specific survival [15]. In the vast majority of small thyroid cancers, cytology does not identify high-risk features or subtypes. Therefore, the rate of disease progression is not known in this setting. Nonetheless, if high-risk features are identified on cytological evaluation, it is reasonable to expect a higher rate of disease progression than has been reported in classic papillary micro-carcinomas.

(d) *Molecular Features*

Papillary carcinomas frequently harbor activating mutations in oncogenes encoding proteins in the MAP kinase pathway. The RET/PTC arrangement has been reported in up to 52 % of PTMC, but unlike PTC it does not appear to be a sign of cancer aggressiveness [7]. Similarly, BRAF mutations have been reported in PTMC; however, results regarding the propensity of BRAF-positive PTMC to develop metastatic foci are mixed [7].

(e) Evidence of Metastases

1. *Lymph Node Metastases*—The incidence of lymph node metastases at the time of PTMC diagnosis is highly variable in the literature and has been reported in anywhere up to 64 % of cases, likely dependent on the extent of prophylactic neck dissection performed [7]. Risk factors identified for nodal metastases in PTMC include non-incidental presentation, larger tumor size (5–10 mm), age >45 years, tumor multifocality, tumor bilaterality, extrathyroidal extension, and the follicular variant

histological subtype [23]. Conversely, the presence of autoimmune thyroid disease appears to be protective against lymph node metastases [26]. However, given the indolent nature of PTMC, it is necessary to draw the distinction between microscopic nodal deposits and clinically significant lymph node metastases. Ito and Miyauchi did not find N1a disease-influenced disease-free survival in patients with PTMC, while N1b disease was associated with significantly worse disease-free survival with a 5-year recurrence rate of 8.5 %[6]. This led the authors to surmise that PTMC with clinically apparent metastases, particularly in the lateral neck, followed a more aggressive course, similar to conventional PTC, than nodal metastases detected only pathologically which do not adversely affect the prognosis of PTMC patients [6]. As in PTC, the size, number, and presence of extranodal extension are markers for disease recurrence and worse prognosis [26].

2. *Distant Metastases*—The presence of distant metastases at the time of diagnosis of PTMC is a rare event. In fact, in an analysis of studies published between 1966 and 2008, there were only 35 reported cases of distant metastases from PTMC (0.37 %) reported [7]. As a result, few studies have evaluated the potential risk factors to predict distant metastatic spread. However, an association between distant disease and tumor size, advanced age, the presence of lymph node metastases at diagnosis, and the follicular variant histological subtype has been reported.

Optimal Surgical Management for Papillary Thyroid Microcarcinoma

Total thyroidectomy and lobectomy are generally low-risk procedures when performed by high-volume surgeons; however, there are inherent potential adverse risks. While the rates of these events are low, in a cohort of patients who already have a low risk of negative outcomes, a 1–2 % risk of permanent vocal cord injury and 2–3 % risk of permanent hypoparathyroidism represent significant odds that may negate any potential benefit (Fig. 10.1). In addition, total thyroidectomy and occasionally lobectomy commit the patient to lifelong thyroid hormone replacement therapy. Further, despite adequate hormone supplementation, many patients report persisting symptoms that negatively impact quality of life, including fatigue, weight gain, and depressed mood, for which the underlying mechanism remains unclear. Moreover, surgical resection does not circumvent the need for long-term surveillance for disease recurrence. Taking into account the low-risk nature of PTMC, it becomes clear that when offering immediate surgical resection to patients indiscriminately, the potential adverse effects and consequences of surgical management outweigh the risks of the disease. In its revised 2015 guidelines, the American Thyroid Association recommends the consideration of active surveillance as an alternative to immediate surgical resection in patients with very low-risk tumors, such as PTMC, in the absence of invasion, metastases, and cytological or molecular markers for aggressive disease [28].

In cases where surgery is preferred, the extent of initial surgery (total thyroidectomy versus lobectomy) does not appear to influence mortality or recurrence rates. In a SEER registry analysis of nearly 8000 patients with PTMC who had undergone lobectomy or total thyroidectomy, nonmetastatic PTMC was found to generally confer an excellent prognosis independent of the extent of resection [19]. Similarly, in an analysis of 867 consecutive, surgically treated patients with small thyroid tumors, Noguchi et al. concluded that lobectomy was sufficient in the majority of PTMC cases [29]. Lee et al. also reported comparable long-term mortality and locoregional recurrence rates in PTMC patients treated by lobectomy with central compartment neck dissection compared to total thyroidectomy with central neck dissection, leading the authors to suggest that in low-risk PTMC completion, thy-

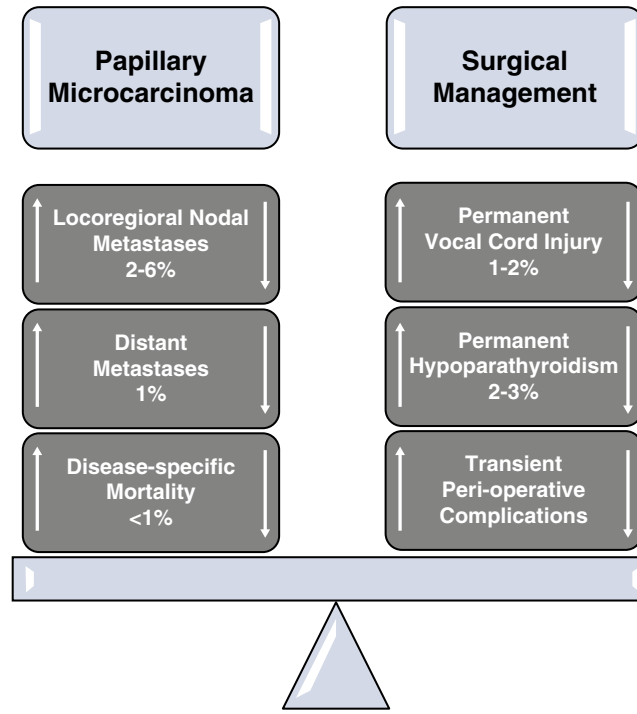

Fig. 10.1 Is the cure worse than the disease? Adverse effects of surgical management of papillary thyroid microcarcinoma versus outcomes following surgical management [13, 14, 27]

roidectomy is not required unless locoregional recurrence is subsequently detected [22]. Moreover, tumor size (≤5 mm versus >5 mm) has not been demonstrated to be a useful determinant of the extent of surgery [22]. Consequently, in cases of unifocal, intrathyroidal PTMC with no clinically detectable lymph node metastases, family history of thyroid cancer, or prior head and neck irradiation where surgical resection is chosen, lobectomy alone is sufficient [19, 28, 29]. A similar approach is recommended when PTMC is detected incidentally following the surgical management of benign thyroid disease. In such cases, the guidelines issued by both the European Society for Medical Oncology and the American Thyroid Association are in agreement that completion thyroidectomy is not required [28, 30].

Prophylactic neck dissection is not required in noninvasive, clinically node-negative PTMC [28]. Although the prevalence of microscopic metastases in cervical lymph nodes is relatively frequent in autopsy and surgical series, prophylactic lymph node clearance needs to be balanced against the clinical significance of microscopic nodal disease and the potential adverse risks of the procedure. Consequently, therapeutic neck dissection is not required unless macroscopic lymph node metastases are identified [29].

Radioactive Iodine Therapy in Papillary Thyroid Microcarcinoma

As with any treatment, the decision to administer RAI should be made only after judiciously weighing the benefits against the risks. The lack of data demonstrating efficacy of adjuvant RAI in PTMC coupled with the potential for adverse risks provides a compelling argument for limiting the use of RAI in this patient population. While these risks may be justifiable in patients with high-risk thyroid cancer where the benefits of RAI therapy are clear, the risk-benefit ratio is less favorable in intermediate- and certainly low-risk patients. Consequently, in the 2009 revision of

their thyroid cancer guidelines, the American Thyroid Association advised that there are no data to support the routine use of RAI in patients with intrathyroidal tumors measuring <10 mm regardless of multifocality and that it should be reserved for cases complicated by nodal or distant metastases [28]. The National Comprehensive Cancer Network guidelines concur, stating that for classical PTC measuring <10 mm that is either unifocal or multifocal, clinical stage N0 and M0, with no vascular invasion, and with an appropriate postoperative Tg, surgical resection is considered a definitive therapy and RAI is not recommended [31].

TSH-Suppressive Thyroid Hormone Replacement Therapy in Patients with Papillary Thyroid Microcarcinoma

In patients already at low risk of disease recurrence, any small potential benefit derived from TSH suppression is outweighed by the risk of adverse effects, specifically atrial fibrillation in the elderly and accelerated bone loss predisposing to osteopenia and osteoporosis. A prospective study found that disease-free survival for low-risk patients managed without TSH-suppressive thyroid hormone replacement therapy was equivalent to those managed with TSH suppression [32]. In addition, an observational study found increased all-cause cardiovascular mortality in patients with WDTC compared to the control population, with a lower survival identified when TSH was maintained below 0.02 mU/L [33]. These considerations are particularly important in very low-risk patients, such as the vast majority of those with PTMC, who have a favorable prognosis from the outset. Consequently, in such patients with an excellent response (no biochemical, clinical, or structural imaging evidence of disease recurrence) or indeterminate response to therapy, the serum TSH may be kept in the low reference range (0.5–2.0 mU/L) [28]. In patients who have undergone lobectomy alone, thyroid hormone supplementation aiming for supernormal T4 levels to achieve TSH suppression is not recommended.

What Is the Recommended Surveillance for Papillary Thyroid Microcarcinoma Recurrence?

Recurrence rates following the definitive treatment of PTMC are low, occurring locoregionally in 2–6 % and distally in 1–2 % of cases [13, 14]. Surveillance for recurrence following surgical resection is generally recommended every 6–12 months, with recurrent disease occurring at a mean of 2.8 years post-initial therapy. As the majority of recurrences are locoregional, neck US is the structural imaging surveillance modality of choice in combination with unstimulated serum Tg and anti-Tg antibody measurement [29].

Active Surveillance

What Is Active Surveillance?

Active surveillance is a proactive management approach with curative intent in which surgical intervention is delayed, while the cancer is actively monitored until evidence of significant disease progression occurs. This is distinct from watchful waiting, a term sometimes erroneously used interchangeably with active surveillance. Watchful waiting refers to a palliative management approach that involves withholding aggressive management and monitoring for symptoms, which are then treated with palliation. Conversely, active surveillance is based on the assumption that a delay in initial therapy has no impact on disease outcomes.

The application of active surveillance to patients with PTMC is a treatment approach that has been adapted from the treatment of similar indolent cancers where it has also been shown to be effective. In prostate cancer, the introduction of screening with serum prostate-specific antigen (PSA) measurement led to the diagnosis of early, indolent forms of the disease. Around half these

prostate cancers never become clinically significant if left untreated, yet up to 90 % of patients undergo definitive surgical management with its inherent significant risks but no clinical benefit [34]. As a result, active surveillance was introduced as an alternative standard of care for low-risk prostate carcinoma.

Arguments in Favor of Active Surveillance in Papillary Thyroid Microcarcinoma

The major clinical impact of active surveillance is in avoiding unwarranted surgery, radioactive iodine administration, unnecessary morbidity, and thyroid hormone replacement in the thousands of patients diagnosed with PTMC each year. Two groups from Japan have published prospective clinical trials documenting their experience with active surveillance in PTMC demonstrating its safety and efficacy.

Ito et al. monitored 340 patients with PTMC for a mean of 74 months. Tumor enlargement (≥3 mm) was observed in 6.4 % and 15.9 % of patients at 5 and 10 years of follow-up, respectively. Novel nodal metastases occurred in 1.4 % of patients at 5 years and 3.4 % at 10 years. There were no instances of distant metastatic disease detected and no thyroid cancer-related deaths. Patients who were subsequently treated with surgical resection, including those with tumor enlargement and nodal metastasis, remained free of recurrence at the end of the follow-up period, indicating that delayed surgery did not alter outcome [16]. More recently, the same group reported outcomes in 1235 cases of PTMC managed with active surveillance for an average follow-up period of 60 months. By the 10-year time point, tumor growth had occurred in 8.0 %, novel lymph node metastases in 3.8 %, and progression to clinical PTC (defined as tumor enlargement to ≥12 mm or development of nodal metastasis) in 6.8 % of subjects. Of the 93 patients who eventually underwent surgical resection, one developed local thyroid bed recurrence. Once again there were no patients in whom distant metastatic disease was detected and no cases of disease-specific mortality [17].

Sugatani et al. actively surveyed 230 patients and at 5 years also observed PTMC stability in the vast majority (90 %), decreased tumor size in 3 %, and enlargement in 7 %. There were no apparent cases of extrathyroidal invasion or distant metastasis, while nodal metastases were detectable in 1 %. In the nine patients who went on to have surgical management, no recurrences had been identified postoperatively [15].

Based on the compelling Japanese data, the Head and Neck Disease Management Team at Memorial Sloan Kettering Cancer Center implemented an active surveillance program as an alternative to immediate surgical resection in selected patients with subcentimeter, intrathyroidal tumors cytologically confirmed as PTC or suspicious for PTC on FNAB. Preliminary rates of disease progression thus far appear in keeping with those previously reported [15, 16].

Arguments Against Active Surveillance in Papillary Thyroid Microcarcinoma

Despite the available evidence supporting the safety and efficacy of active surveillance in PTMC as an alternative to immediate surgical management, it is yet to be widely adopted in clinical practice outside of the Japanese setting. This is due in part to hesitancy by clinicians to manage PTMC conservatively and being unduly influenced by a small subset of patients with poor outcomes highlighted in prominent case reports in the literature [18, 35–42]. While distant metastases and death may very rarely occur from PTMC, the infrequency of such events is evident when these case reports are weighed against the prospective active surveillance data previously presented [15–17].

Ongoing investigations and follow-up reviews may also be considered a disadvantage of observational management. However, continued surveillance for disease recurrence following definitive surgical resection is still required. In addition, there is a perception that a nonsurgical management approach will not appeal to patients. This has not been the experience at Memorial Sloan Kettering Cancer Center where approximately

88 % of selected patients with PTMC elect to undergo active surveillance when presented as a standard of care option alongside immediate surgical resection [43]. After a mean follow-up period of 12 months, high retention rates have been observed with 95 % of patients remaining on active surveillance with stable disease [43].

Active Surveillance Protocol for Papillary Thyroid Microcarcinoma

Patient Selection for Active Surveillance

As in other therapeutic modalities in thyroid cancer, patient risk stratification prior to undertaking active surveillance is imperative. In the study by Ito et al. [16], active surveillance was offered to patients with PTMC that did not have any of the following features:

(a) Location—adjacent to the trachea or the dorsal surface of the thyroid close to the recurrent laryngeal nerves
(b) Cytology—findings suggestive of high-grade malignancy on FNAB
(c) Nodal Metastases—evident regional lymph node metastases
(d) Progression to Clinical Disease—signs of progression during follow-up

The presence of the risk factors associated with lymph node metastases previously outlined does not necessarily preclude active surveillance due to their lack of predictive power. However, these patients should be followed more closely and a lower threshold for shifting to surgical management be observed.

How to Approach Active Surveillance with the Patient

When discussing observational management with patients, it is essential to have an understanding of the psychosocial factors that influence the treatment decision-making process and the potential barriers toward the acceptance of an active surveillance approach. In a prospective study of patients with localized prostate cancer designed to gain insight into the rationale underlying treatment decisions, posttreatment satisfaction was high regardless of whether patients elected to undergo active surveillance or radical prostatectomy, with nearly 93 % of patients indicating they would make the same choice again [44]. This demonstrated that patients have clear motivations for selecting their treatment of choice.

Patients with a preference for surgical management of PTMC tend to have an emotion-based rather than disease-focused treatment decision-making process that is founded in fear and anxiety. The reason most frequently reported by prostate cancer patients for rejecting active surveillance was a fear of future consequences [45]. Concerns regarding tumor progression and metastatic spread bring about a sense of urgency for the physical removal of all traces of cancer from the body. In addition, some patients have the misconception that surgery is the inevitable outcome or that surgical resection will obviate the need for any ongoing follow-up.

On the other hand, patients who opt for active surveillance appreciate the indolent nature of the disease and have a desire to preserve normal thyroid gland function, expressing a fear of being reliant on thyroid hormone replacement. In addition, they tend to acknowledge the potential surgical risks and are comfortable in the knowledge that surgical resection can be reconsidered at any point during follow-up.

Hesitancy to adopt an active surveillance approach in PTMC on the part of either the clinician or the patient may arise from misconceptions surrounding the nature of the disease, an overestimation of the effect of treatment, and a lack of appreciation for the true risk-benefit ratio of surgical management. Barriers to the uptake of active surveillance by the patient include anxiety in response to a perceived lack of intervention, uncertainty related to a sense of loss of control, lack of patient education and support particularly at the time of initial treatment planning, and a

failure by the treating practitioner to present active surveillance as a treatment option alongside surgical resection. Approaches that have been identified to address these barriers include increased education, improved communication, interventions to reduce feelings of uncertainty and anxiety (e.g., cognitive reframing), as well as empowering patients with a sense of control through inviting them to become active participants in their management.

In another survey of patients with low-risk prostate cancer, those who enrolled in active surveillance most frequently cited physician influence as the greatest contributing factor to their treatment choice [46]. This highlights the need to reeducate ourselves based on the available data to improve our ability to aid patients in making fully informed decisions about the treatment choice that is right for them. All patients must be equipped with an accurate understanding of the potential risks and benefits of each treatment option, including active surveillance. This requires time spent in educating the patient about the data in order to counter a lifetime of conditioning that cancer is necessarily incompatible with life—an essential part of addressing the inherent uncertainty of living with an untreated cancer [47]. Psychosocial interventions may also be required to support patients and their families undergoing active surveillance, with peer-support groups having been reported to be of particular value. These measures need to be tailored to the needs of the individual with some patients requiring more support, particularly in the early stages of active surveillance, than others.

Recommended Active Surveillance Protocol

An algorithm outlining the recommended protocol for active surveillance in PTMC is shown in Fig. 10.2. Patients with PTMC who enter the active surveillance program are monitored on a

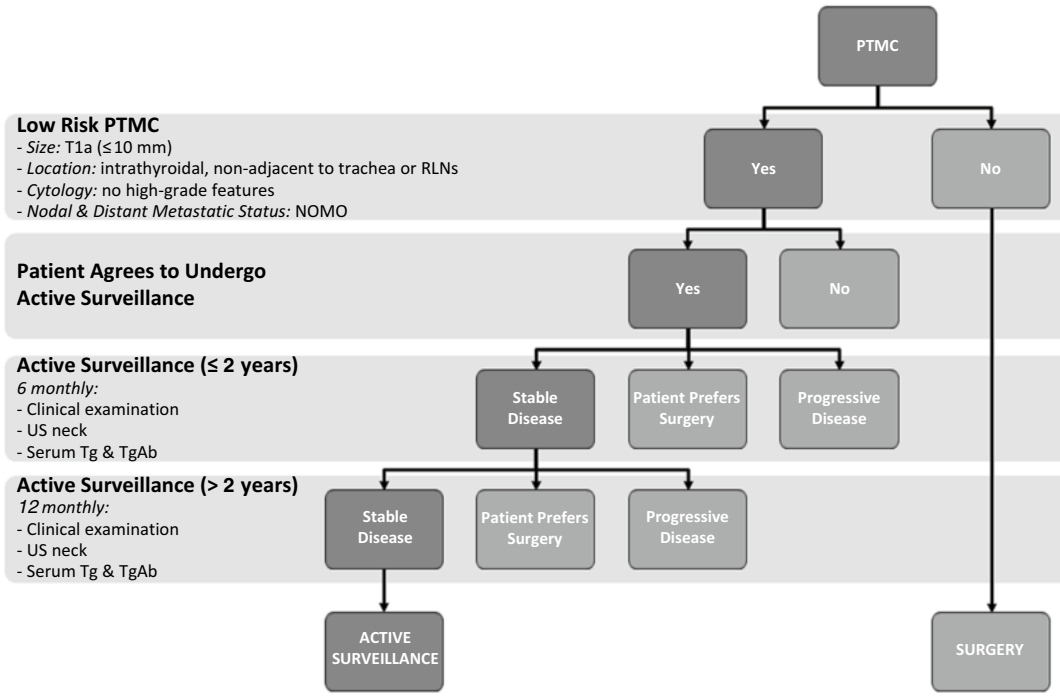

Fig. 10.2 Recommended treatment algorithm for patients with papillary thyroid microcarcinoma (*PTMC* papillary thyroid microcarcinoma, *FNAB* fine-needle aspiration biopsy, *US* ultrasound, *RLN* recurrent laryngeal nerve, *Tg* thyroglobulin, *TgAb* anti-thyroglobulin antibody)

six-monthly basis for the initial two years or until disease stability is established at which point the interval between surveillance visits is gradually increased to 9–12 months. At each visit patient disease status is assessed by:

(a) Physical examination
(b) Serum thyroglobulin (Tg) and anti-Tg antibody measurement
(c) TSH
(d) Neck US

US is invaluable in monitoring for disease progression during active surveillance, allowing assessment of the primary tumor and evaluation for novel nodal metastases [6]. An increase in the size of the index lesion by ≥3 mm in any dimension compared to baseline and confirmed on a subsequent US performed 2–6 months later is required to establish PTMC growth. This 3 mm threshold takes into account the margin of error associated with US measurements and has been demonstrated to be safe and reproducible in previous prospective trials of active surveillance [15, 16]. Tumor growth must be verified on a subsequent US (usually 2–3 months later) to offset measurement error and allow for fluctuations in tumor size that have been observed in the literature [6]. Due to the operator-dependent nature of sonography, surveillance US should be performed in one center by staff experienced in thyroid US in order to minimize inter-scan variability.

The typical US features of metastatic lymph nodes have been previously described by Antonelli et al. and are presented in Table 10.2. The positive predictive value of US for the diagnosis of nodal metastasis is >80 % [48]. Although the sensitivity of US for detecting lymph node metastases in the central compartment is lower (~10.5 %) due to structural interference from the thyroid gland and trachea, an association with central nodal metastases and reduced disease-free survival has not been identified. In the event that a lymph node suspicious for metastasis by US criteria is detected, confirmation with US-guided FNAB with Tg washout is required [6].

If at any stage during active surveillance there is evidence of progression to clinically significant disease (i.e., confirmed tumor growth to >10 mm in size, evidence of extrathyroidal extension, or development of cytologically confirmed nodal metastases) or the patient opts for surgery irrespective of lesion stability, surveillance should be terminated and the patient referred for definitive surgical management as previously described. The decision to proceed with surgery needs to be balanced against the comfort of the patient, medical practitioner, and the quality of surveillance investigations available.

Table 10.2 Ultrasound characteristics suspicious for lymph node metastases in thyroid cancer

Feature	Suspicious findings on ultrasound
Shape	Round
Echogenicity	Hyperechoic
Hilum	Absent
Consistency	Cystic change
Inclusions	Calcifications
Vascularity	Increased (peripheral and central)

Future Directions

Development of Robust Predictors of Disease Outcome

The overdiagnosis of subclinical PTC presents the healthcare community with the challenge of differentiating between the minority of patients who will benefit from early definitive surgical management from those who may be spared invasive therapy and its attendant risks. Unfortunately, there is no single clinical or molecular feature that can as yet reliably identify the small number of patients with PTMC that will go on to develop clinically significant disease. Even when used in combination, negative clinical features have a positive predictive value and specificity too low for use in preoperative risk stratification. Histopathological markers of negative PTMC outcomes identified in retrospective studies are also of limited clinical value given they require assessment of the postoperative specimen. Similarly, a number of mutations in tumor oncogenes have been associated with increased risk of locoregional lymph node metastases, but

individual marker status alone has insufficient power to be predictive. Though the risk of disease progression and metastasis of PTMC remaining in situ are low, the development of clinical, cytological, and molecular factors that are robustly associated with the likelihood of progression to significant disease and which could be obtained preoperatively would improve patient and physician confidence in adopting an observational management approach.

Pushing the Boundaries: Defining the Safe Size Threshold for Active Surveillance

Further research is required to ascertain the safety of offering active surveillance to patients with small PTC, for example, ≤15 mm in size. The 10 mm size cutoff for PTMC is somewhat arbitrary, and it is biologically plausible that a subset of PTC larger than this threshold also exhibit indolent behavior. The implications of this premise are only fully appreciated when one recognizes that 87 % of the rise in thyroid cancer incidence in the United States was accounted for by PTC ≤20 mm in size [2].

Conclusions

In the setting of a changing thyroid cancer landscape, it is necessary to adapt treatment strategies to provide early definitive management for high-risk patients while avoiding overtreatment and its incumbent adverse effects in those with low-risk disease. Active surveillance is a safe and effective alternative to immediate surgical resection in well-selected patients with low-risk PTMC. It is an attractive management approach to patients, their families, and referring medical practitioners that should be presented as a reasonable alternative to immediate surgical resection. In cases where surgery is desired, the vast majority of low-risk PTMC can be adequately treated with lobectomy alone, without the need for adjuvant RAI. Ultimately, the optimal management of PTMC requires a balanced discussion between physician and patient encompassing all available treatment strategies with their associated advantages and disadvantages to facilitate the formulation of therapeutic plan individualized to the patient.

Disclosures The authors have no relevant conflicts of interest to disclose.

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11 Molecular Profiles and the "Indeterminate" Thyroid Nodule

Alireza Najafian, Aarti Mathur, and Martha A. Zeiger

Introduction

Fine-needle aspiration (FNA) biopsy is the most accurate and reliable diagnostic test available for the evaluation of a thyroid nodule. However, 20–30 % of FNA results are indeterminate or suspicious, and of those resected, 10–40 % are confirmed to be malignant on final pathology [1–3]. In order to improve upon the diagnostic accuracy of FNA, ancillary molecular tests have emerged to help preoperatively distinguish between benign and malignant nodules. However, the clinical utility of these tests and implications for optimal patient management are not well established. This review will focus on the efficacy of these molecular markers in thyroid nodule diagnosis, specifically when a marker(s) might provide added benefit and how to potentially incorporate these results.

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Accuracy of FNA

Although FNA is the gold standard for diagnosis of a thyroid nodule, its accuracy and reproducibility vary considerably, mainly because cytologic interpretation is quite subjective. To address this, the 2007 National Cancer Institute Thyroid FNA conference proposed the Bethesda System for Reporting Thyroid Cytopathology (TBSRTC) in an attempt to standardize diagnostic terminology and improve the clinical utility of FNA. This six-tiered system is comprised of the following diagnoses: nondiagnostic, benign, atypia of undetermined significance (AUS), follicular neoplasm or suspicious for follicular neoplasm (FN/SFN), suspicious for malignancy (SFM), and malignant [4]. The proposed risk of malignancy for each indeterminate and suspicious category is as follows: AUS, 5–15 %; FN/SFN, 15–30 %; and SFM, 60–75 %. Based on these risks, the recommended management for AUS is a repeat FNA; for SFN/FN, surgical lobectomy; and SFM, total thyroidectomy or lobectomy. We know however that these rates of malignancy are not consistent across clinical practices, thus challenging these clinical recommendations [5]. For example, we and others have demonstrated the risk of malignancy associated with AUS to be as high as 39 %, and thus our group recommends surgery as opposed to repeat FNA [5–8]. Furthermore, significant intra- and interobserver variation in cytological diagnosis also occurs.

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When 3885 thyroid outside cytological specimens were rereviewed at our institution, the diagnosis changed 32 % of the time [9]. As a consequence, and despite the TBSRTC, this degree of variation in cytological diagnoses still exists and further emphasizes the need for ancillary, more definitive diagnostic testing. Research over the past decade suggests that molecular markers may add diagnostic value to an indeterminate or suspicious FNA biopsy.

The Gold Standard in Diagnosis

The gold standard in the diagnosis of a thyroid nodule is histopathology, and thus, the accuracy of FNA cytology or any molecular test is based on the final diagnosis. However, significant intra- and interobserver variation also exists in making histopathologic diagnoses, and studies have reported disagreement rates as high as 21 % [10, 11]. This variation more typically arises when evaluating follicular lesions. Although histopathologic definitions exist, distinguishing follicular variant of papillary thyroid cancer (FVPTC) from follicular carcinoma or a follicular adenoma can be difficult, especially if nuclear features of papillary carcinoma are not well developed or only focally present. The absence of clear diagnostic criteria for FVPTC has led to an overcalling of this malignant diagnosis. Furthermore, the lack of consensus on the definition of capsular invasion makes diagnosing a benign adenoma versus a follicular carcinoma difficult. Therefore subjective variation in the diagnoses of follicular lesions complicates the evaluation of a molecular test for an indeterminate thyroid nodule, as the accuracy of the test relies on an accurate and consistent histologic diagnosis.

Molecular Markers

Rapidly Accelerated Fibrosarcoma Isoform B

Rapidly accelerated fibrosarcoma isoform B (BRAF) is one of the three *RAF* paralogs (*ARAF*, *BRAF*, and *CRAF*) and is the most potent activator of the mitogen-activated protein kinase (MAPK) pathway [12]. As one of the most common protein kinase gene mutations in all human malignancies, *BRAF* is found in 7 % of all cancers and is the most studied molecular marker in thyroid cancer [13, 14]. It occurs in 27.3–87.1 % of papillary thyroid cancer (PTC), 35 % of FVPTC, and 25 % of anaplastic thyroid cancers [15–20]. *BRAF* mutation is not, however, present in pure follicular thyroid cancers, medullary thyroid cancers, or benign tumors. Given the high prevalence of this mutation in PTC, *BRAF* has been widely investigated to determine whether its detection can improve upon the diagnostic accuracy of indeterminate thyroid FNA. Most studies demonstrate that, although it is a highly specific test (100 % specific), it has relatively low sensitivity, ranging from 15 to 45 % for indeterminate/suspicious nodules [21–24]. *BRAF* V600E mutation fails to detect a high proportion of malignant lesions with initially indeterminate or suspicious cytology, an important consideration to take into account when examining the efficacy of *BRAF* testing in thyroid nodule diagnosis [25].

Mutation/Rearrangement Panel

Over the last three decades, multiple mutations and chromosomal translocations have been identified in thyroid cancer. More than 70 % of PTCs carry mutually exclusive mutations or chromosomal translocations in genes that activate the MAPK or the PI3 kinase/AKT signaling pathways and include *BRAF*, *RAS*, *RET/PTC*, and *TRK* rearrangements (Fig. 11.1). Similarly, mutations in the *RAS* gene or rearrangement of *PAX8/PPARγ* have been detected in 70–75 % of follicular carcinomas [26]. Due to the limited diagnostic utility of a single molecular marker, a somatic mutation panel including *BRAF*, *RAS*, *RET/PTC*, and *PAX8/PPARγ* rearrangement was evaluated to predict the likelihood of malignancy in a thyroid nodule. Most recently, The Cancer Genome Atlas (TCGA) program sponsored by NCI, NIH has reported on their comprehensive analysis of approximately 500 PTCs. The study revealed two distinct PTC subtypes, one primarily *BRAF*-like and another primarily *RAS*-like, with the *RAS*

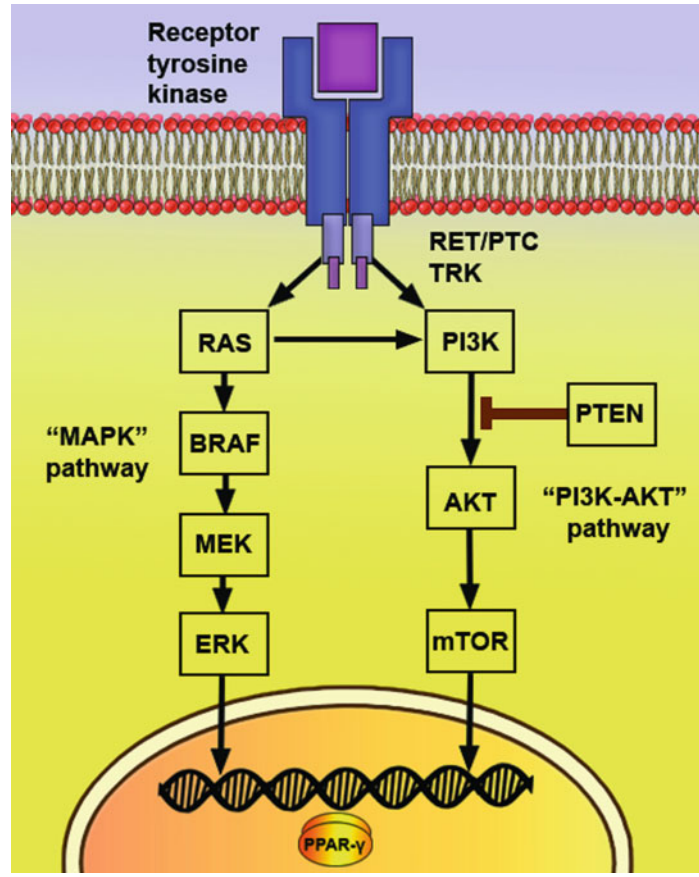

Fig. 11.1 The MAPK and PI3-AKT pathways. Dysregulation of the MAPK or the PI3K-AKT pathways is involved in thyroid carcinogenesis. The MAPK pathway is frequently activated in thyroid cancer via point mutations of *BRAF* and *RAS* genes (or chimeric fusion proteins RET/PTC), and the PI3K pathway is frequently activated via point mutations of *PIK3CA* and mutation/deletion of *PTEN*. *RAS* rat sarcoma, *BRAF* rapidly accelerated fibrosarcoma isoform B, *MAPK* mitogen-activated protein kinases, *MEK* mitogen-activated protein/extracellular signal-regulated kinase kinase, *ERK* extracellular signal-regulated kinases, *PI3K* phosphatidylinositol 3-kinase, *PTEN* phosphatase and tensin homologue, *mTOR* mammalian target of rapamycin, *PPAR-γ* peroxisome proliferator-activated receptor gamma

tumors having more follicular features [27]. Additional molecular changes, including copy number variation, chromosomal translocations, and other less frequent molecular changes, have been identified, and the majority of which are mutually exclusive. This very comprehensive study sets the stage for the likelihood of future histologic reclassification of PTCs.

Nikiforov et al. performed one of the earliest studies evaluating the feasibility and role of a mutation panel [28]. They prospectively correlated cytology, mutational status, and either surgical pathology or follow-up for an average of 34 months in 470 FNA specimens, of which 51 samples had indeterminate cytology. All mutation-positive cases of AUS, FN/SFN, and SFM were malignant at surgery, and therefore the panel had 100 % specificity. However, the sensitivity and accuracy for these 51 samples was 100 % for the 21 AUS samples; 75 % and 87 % for 23 SFN samples; and 60 % and 71 % for 7 SFM samples, respectively. The authors concluded that the panel improved the diagnostic accuracy of cytology alone as the cancer probability for indeterminate cytology increased to 100 % with a positive molecular test result, and those patients would therefore be strong candidates for a total thyroidectomy.

Subsequently, a large multi-institutional prospective analysis of 513 consecutive thyroid FNA samples with indeterminate or suspicious cytology demonstrated high specificity and positive predictive value for this panel [29]. The risk of malignancy with any mutation detected was 88 % for the AUS category, 87 % for SFN, and 95 % for the category of SFM. However, the risk of malignancy of a nodule that had no mutation was 6 % for AUS, 14 % for SFN, and 28 % for

SFM. Although the specificity was greater than 96 % in the indeterminate categories, the sensitivity ranged from 57 to 68 % (Table 11.1).

Cantara and colleagues evaluated the impact of somatic mutations, including *BRAF*, *RAS*, *RET*, *TRK*, and *PAX/PPARγ*, on cytology in 235 thyroid nodules [30]. Cytology alone had a sensitivity of 59 %, a specificity of 94.9 %, and an accuracy of 83 %. With the addition of molecular testing, the sensitivity increased to 89.7 %, specificity was 94.9 %, and accuracy was 93.2 %. The addition of molecular markers in this study improved sensitivity and accuracy, but added nothing to the specificity of cytology. The authors included 87 nodules with benign cytology in addition to 53 nodules with inadequate cytology. Thus, the significance of an added benefit is difficult to determine from this study. From these studies one can conclude that although the somatic mutation panel is highly specific, its main limitation is sensitivity. Without incorporation into a decision analysis tool, its clinical utility overall still remains unclear, especially given the fact that there is tremendous variability in both cytologic and pathologic diagnosis from one pathologist to another and one institution to another.

Afirma®

An alternative approach for classifying indeterminate nodules is the commercially available gene expression classifier (GEC) panel, Afirma® (Veracyte). It measures expression of 142 genes representing well-known cancer biologic pathways. In contrast to the somatic mutation panel and *BRAF* testing, which are both positive predictors of malignancy, this test was designed to improve the negative predictive value (NPV) and in turn reduce or eliminate the need for diagnostic surgery. The company, Veracyte, requires two sets of FNA samples, one for cytological evaluation and the other for gene expression profiling. The second sample only undergoes GEC if the cytology is read as AUS or FN/SFN.

Two large prospective studies were the first to evaluate this test. In a preliminary study, Chudova and colleagues [31] measured more than 247,186 transcripts in 315 thyroid nodules to create a molecular panel to distinguish benign and malignant thyroid nodules. An algorithm, the Afirma GEC, was generated to identify nodules as benign or suspicious and was tested using an independent set of 24 indeterminate FNA samples. The NPV and specificity of this test were estimated to be 96 % and 84 %, respectively.

Subsequently, in an industry-sponsored prospective, multicenter study of 265 nodules with indeterminate cytology, Alexander and colleagues validated the clinical utility of this algorithm [32]. In this study, thyroidectomy was performed on the basis of the clinical judgment of the treating physician at each site without knowledge of the GEC test results. Histopathologic diagnosis was rendered by a central panel of blinded academic endocrine pathologists and served as the reference standard for clinical validation. Of the 265 nodules, 85 (32 %) were malignant. For each Bethesda category, the sensitivities were as follows: AUS, 90 %; FN/SFN, 90 %; and SFM, 94 %; whereas the specificities were lower: AUS, 53 %; FN/SFN, 49 %; and SFM, 52 %. The NPV for each indeterminate category was as follows: AUS 95 %, SFN 94 %, and SFM 85 %. The overall sensitivity for indeterminate nodules was 92 %, and the specificity was 52 %. The overall NPV was 7 %, which is similar to the NPV for benign cytology alone. Based upon this study, half of benign nodules with indeterminate cytology could be diagnosed preoperatively with this test and surgery avoided in this population of patients.

The above studies did not distinguish Hürthle cell-rich nodules from other types of indeterminate nodules. Several recent small studies using this test in routine clinical practice have differentiated this subset, noting a difference in GEC results [33–35].

Lastra and colleagues retrospectively examined a cohort of 132 indeterminate nodules that had Afirma® testing [33]. They reported that the test classified only 8 of 25 (32 %) cases with the cytologic diagnosis of follicular neoplasm with oncocytic features (FNOF) as benign, whereas 45 of 68 cases (66 %) of AUS and 17 of 39 (44 %) of FN were read as benign [36]. Forty-eight patients

Table 11.1 Summary of sensitivity, specificity, and accuracy of different molecular markers in indeterminate thyroid nodules

Author (year)	Molecular marker	Indeterminate/total	Sensitivity (%)	Specificity (%)	Accuracy (%)
Mutation/rearrangement panel					
Nikiforov et al. (2009)	*BRAF, RAS, RET/PTC, PAX8/PPARγ*	51/470	60–100	100	71–100
Cantara et al. (2010)	*BRAF, RAS, RET, TRK, PPRγ*	41/235	90	95	93
Nikiforov et al. (2011)	*BRAF, RAS, RET/PTC, PAX8/PPARγ*	1056/1056	57–68	96–99	81–94
Afirma®					
Chudova et al. (2010)	Afirma®	24/315	86	40	N/A
Alexander et al. (2012)	Afirma®	265/4812	92	52	N/A
NGS					
Nikiforov et al. (2014)	ThyroSeq v2 (AKT1, *BRAF, RAS, PIK3CA, TP53, TSHR, PTEN, GNAS, CTNNB1, RET, TERT*)	143/143	90	93	92
Mercier et al. (2014)	*ABL1, AKT1, ALK, APC, ATM, BRAF, CDH1, CDKN2A, CSF1R, CTNNB1, EGFR, ERBB2, ERBB4, EZH2, FBXW7, FGFR1, FGFR2, FGFR3, FLT3, GNA11, GNAQ, GNAS, HNF1A, HRAS, IDH1, IDH2, JAK2, JAK3, KDR, KIT, KRAS, MET, MLH1, MPL, NOTCH1, NPM1, NRAS, PDGFRA, PIK3CA, PTEN, PTPN11, RB1, RET, SMAD4, SMARCB1, SMO, SRC, STK11, TP53, VHL*	34/34	71	89	85
MicroRNAs[a]					
Nikiforova et al. (2008)	miR-187, miR-222, miR-221, miR-146b, miR-155, miR-224, miR-197	8/62	N/A	N/A	N/A
Kitano et al. (2012)	miR-7	21/59	100	20	37
Shen et al. (2012)	miR-146b, miR-221, miR-187, miR-30d	30/68	63	79	73
Keutgen et al. (2012)	miR-222, miR-328, miR-197, miR-21	72/72	100	86	90

[a]Values on microRNA studies are representative of results from validation sets
N/A Not available

with suspicious Afirma® results underwent surgery, and 11 of 13 (85 %) with FNOF had benign histopathology compared to 7 of 18 (39 %) with AUS and 8 of 17 (47 %) with FN. McIver et al. reported that only 1 of 13 (8 %) nodules with Hürthle cell predominance were read as benign by Afirma® and only 2 of the 12 read as suspicious by Afirma® were malignant on final pathology [35]. Harrell and Bimston retrospectively reviewed Afirma® results of 58 indeterminate nodules, of which 20 were read as benign by the GEC [34]. They noted that 21 of the 58 FNA samples had a predominance of Hürthle cells. Of those, Afirma® read 2 as benign and 19 as suspicious, and yet only 35 % were malignant on final pathology. Afirma® suspicious Hürthle cell-rich lesions were found to have a low rate of malignancy on surgical follow-up. Although these studies have small numbers of patients, they question the performance of the Afirma® for Hürthle cell-rich lesions since the majority will be suspicious on Afirma® testing, but benign on final histopathology.

In summary, based on the low specificity of Afirma®, although it can truly detect approximately half of the benign nodules with indeterminate cytology (true negative), it will mistakenly report the other half of the benign nodules as suspicious (false positive). Several studies suggest that these false-positive results may arise from Hürthle cell-rich lesions, although larger studies are needed to confirm this finding especially since this test is not marketed to use this way.

Next-Generation Sequencing

Although the Afirma® and somatic mutation panels offer some improvement on cytological diagnosis, the ability to preoperatively identify a cancer needs further refinement. The mutation panel relies on the automated Sanger method for genetic sequencing analysis, the dominant method over the past several decades [37, 38]. Recently, next-generation sequencing (NGS) was introduced to enable simultaneous sequencing of multiple genes (targeted sequencing), with as little as 5–10 ng of DNA, in a more cost-effective manner [39–42]. Additionally, NGS can perform whole-genome sequencing, whole-exome sequencing, and whole-transcriptome sequencing [42]. As a result, this method can detect mutations with a higher sensitivity on small tissue samples that would have been otherwise excluded due to quantity limitations [39].

Nikiforova and colleagues used NGS to expand the diagnostic mutational panel from 4 to 12 cancer genes. The targeted NGS panel (ThyroSeq v1) included *BRAF*, *RAS*, *PIK3CA*, *TP53*, *TSHR*, *PTEN*, *GNAS*, *CTNNB1*, *and RET* and was performed on 228 DNA samples, which consisted of samples from 105 snap-frozen tissues; 72 formalin-fixed, paraffin-embedded tissue; and 51 FNA samples. Molecular profiles for the common types of thyroid cancer with point mutations were generated. NGS identified mutations in one of 12 cancer genes in 99 of 145 (68 %) malignant samples. The panel identified mutations in 70 % of PTCs, 83 % of FVPTCs, 78 % of conventional FTCs, 39 % of oncocytic follicular carcinomas, 30 % of poorly differentiated thyroid carcinomas, 74 % of anaplastic thyroid carcinoma, and 73 % of medullary thyroid carcinomas [42]. In contrast, only 6 % of benign nodules were mutation positive. This NGS panel was then modified to create ThyroSeq v2, which detects mutational hotspots in an additional gene, the telomerase reverse transcriptase (TERT) promoter, and 42 types of gene fusions that occur in thyroid cancer. In another study, Nikiforov et al. evaluated 143 consecutive FNA samples with a cytologic diagnosis of FN/SFN from patients with known surgical outcomes [13]. On final histologic analysis, 104 nodules were benign and 39 were malignant. The ThyroSeq v2 NGS panel had 90 % sensitivity, 93 % specificity, a PPV of 83 %, a NPV of 96 %, and 92 % accuracy. The authors concluded that this broad NGS panel provides a highly accurate method to preoperatively identify malignant nodules.

Le Mercier and colleagues utilized NGS to retrospectively analyze 50 gene mutations in 34 indeterminate FNA samples. The histological diagnoses were benign in 27 cases, malignant in 7 cases (3 PTCs, 3 minimally invasive follicular cancers, and 1 follicular tumor of uncertain malignant potential). The authors classified results as molecular test positive, a subgroup with 63 % risk of malignancy, or molecular test negative, a subgroup of patients with 8 % risk of malignancy. The sensitivity of this test was 71 %, and specificity was 89 % with a PPV and NPV of 63 % and 85 %, respectively, and an accuracy of 85 % [38]. Although the authors concluded that NGS was feasible and may improve the diagnostic accuracy of FNA biopsy, the low sensitivity of this test suggests that further refinement of the panel is still necessary in order for it to be ultimately clinically useful.

The well-known association between multiple gene mutations and thyroid cancer and the ability of NGS to detect multiple mutations by analyzing a very small amount of DNA that can be obtained from preoperative FNA raise the hope of development of a sensitive and accurate method to improve the preoperative diagnosis of thyroid cancer. These promising preliminary findings of NGS warrant further investigation with larger prospective studies that carefully evaluate their true clinical utility.

MicroRNA

miRNAs are short 19–23-nucleotide length noncoding single strand RNAs (Fig. 11.2) that were initially described in studies on *Caenorhabditis elegans* in 1993 [14]. They are present in both tissue and the circulation and regulate a number of cellular processes by either upregulating or silencing target genes [43]. The tissue specificity of miRNAs and stability of circulating miRNAs make them suitable choices as potential diagnostic markers of malignancy [44]. Although the exact mechanism is unclear, recent studies have reported dysregulation of several miRNAs in thyroid carcinoma [45, 46], and investigations of various miRNA expression patterns in PTC, FTC, and FVPTC compared with benign tissue have identified several differentially expressed miRNAs [13, 45–49]. However, only few studies have examined the diagnostic utility of these miRNA panels for an indeterminate FNA [50].

One of the earliest studies by Nikiforova et al. investigated the differential expression of a panel of seven miRNAs (miR-187, miR-222, miR-221, miR-146b, miR-155, miR-224, and miR-197) in 60 resected thyroid nodules and then validated their results on 62 FNA specimens [46]. Only 13 patients in the FNA validation group underwent surgery based on atypical cytology (eight patients), malignant cytology (four patients), or clinical suspicion (one patient). On histopathology eight were malignant nodules and five were benign hyperplastic nodules. They found that a twofold upregulation of at least one of these miRNAs was associated with a sensitivity, specificity, and accuracy in diagnosing cancer of 88 %, 94 %, and 95 %, respectively. However, a subgroup analysis of indeterminate FNAs was not performed, likely due to the small sample size.

As the largest miRNA study in indeterminate thyroid nodules to date, Keutgen and colleagues derived a predictive model for an miRNA panel with 101 indeterminate thyroid lesions (29 indeterminate thyroid FNAs and 72 independent validation FNAs) [51]. After model selection, a panel of four miRNAs (miR-222, miR-328, miR-197, and miR-21) was validated on 72 consecutive indeterminate thyroid FNAs, of which 22 were malignant on final pathology. The model correctly classified 65 of the 72 samples, with 100 % sensitivity, 86 % specificity, and 90 % overall accuracy for differentiating malignant from benign thyroid lesions. Of the seven incorrectly predicted lesions, five had a diagnosis of Hürthle cell neoplasm on FNA. After excluding all Hürthle cell lesions, performance of the model improved with a specificity of 95 % and overall accuracy of 97 %. Again, this questions the predictive value of molecular panels in Hürthle cell-rich lesions, which are also one of the main diagnostic challenges for cytologists.

In another study, Kitano and colleagues evaluated expression of miR-7, miR-126, miR-374, and let-7 g in 95 FNA samples, of which 31 had

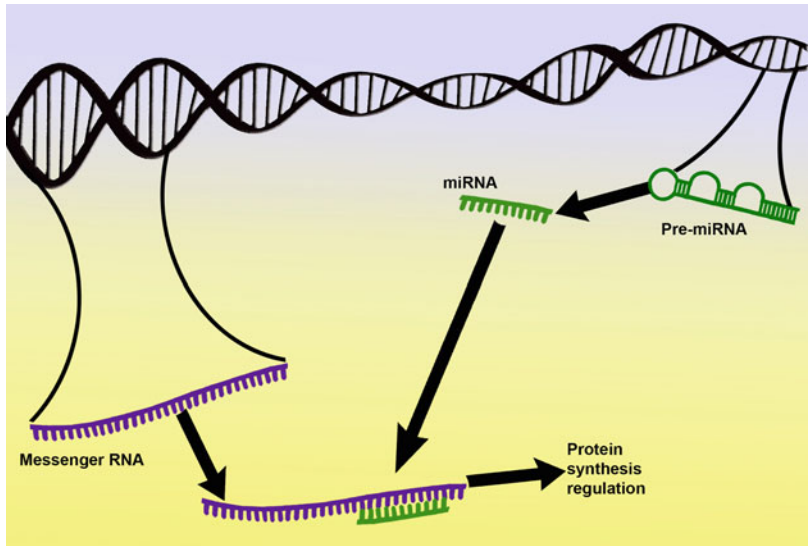

Fig. 11.2 miRNA synthesis and function. miRNAs are small nonprotein-coding single strand RNAs that bind to the untranslated regions of target mRNAs to regulate their translation and stability

indeterminate cytology. From these data they created a thyroid malignancy prediction model [52]. Validation in 59 samples demonstrated downregulation of miR-7 as the only marker that was differentially expressed in malignant thyroid lesions. Overall, miR-7 was 100 % sensitive, 29 % specific, had a PPV of 36 %, NPV of 100 %, and an overall accuracy of 76 %. Subgroup analysis of the 21 indeterminate samples in the validation cohort revealed a sensitivity of 100 %, specificity of 20 %, PPV of 25 %, NPV of 100 %, and overall accuracy of 37 %. Given the high NPV of miR-7, the authors concluded that a patient with a benign miR-7 result could be followed instead of undergoing diagnostic thyroidectomy.

Shen et al. measured the expression of eight miRNAs (miR-146b, miR-221, miR-187, miR-197, miR-346, miR-30d, miR-138, and miR-302c) in 60 indeterminate, suspicious, or malignant FNAs [53]. Evaluation of a validation set of 68 samples confirmed the diagnostic role of four miRNAs (miR-146b, miR-221, miR-187, and miR-30d) in the differentiation of benign from malignant lesions with a sensitivity of 88.9 %, specificity of 78.3 %, and accuracy of 85.3 %. After subgroup analysis of 30 cases with atypia, the diagnostic accuracy dropped to 73.3 % with a sensitivity and specificity of 63.6 % and 78.9 %, respectively. This group noted that while their panel of miRNA could accurately identify PTC, it was inaccurate for follicular tumors, which unfortunately generally comprise the majority of indeterminate FNAs.

Dettmer et al. evaluated the role of miRNA expression in differentiating conventional FTC (cFTC) from oncocytic FTC (oFTC) [54]. They found that a novel miRNA, miR-885-5p, was upregulated (>40-fold) in oFTCs, but not in cFTC. A classification and regression tree algorithm applied to additional 19 indeterminate FNA samples demonstrated that three dysregulated miRNAs including miR-885-5p, miR-221, and miR-574-3p could differentiate follicular thyroid carcinomas from benign hyperplastic nodules with 100 % diagnostic accuracy. Although they evaluated a small sample size of indeterminate lesions, this study introduced an miRNA panel that may accurately discriminate between follicular carcinomas and hyperplastic nodules.

Several of the above studies are promising. Further larger prospective studies, however, are needed to compare various miRNAs and panels to determine a signature for each type of thyroid cancer prior to clinical application.

Surgical Decision-Making

Although molecular markers may improve upon the diagnostic accuracy of FNA biopsy, their true impact on surgical decision-making remains unclear. In clinical practice, the decision to proceed with surgery and choice of surgical procedure reflects a multitude of clinical considerations. Often times, patient preference or clinical variables, such as nodule size, presence of compressive symptoms, family history, or other risk factors, impact the process of decision-making for an indeterminate thyroid nodule (Fig. 11.3). Furthermore, they also may have other indications for a total thyroidectomy, again challenging the impact that a molecular marker or panel may actually have.

Two studies have evaluated the clinical impact of Afirma® on operative decision-making. In a multicenter study on 339 patients with an indeterminate cytology (165 AUS, 161 FN, and 13 SFM) who underwent Afirma® testing, the effect of the GEC on operative decision-making was evaluated [55]. This study, conducted over a 3-year period, included patients from five academic medical centers. Among the 339 patients, surgery was initially recommended in 4 out of 174 (2 %) patients with a benign GEC, 141 out of 148 (95 %) patients with a suspicious GEC, and 4 out of 17 (34 %) patients with nondiagnostic result. However, due to other factors such as additional clinical features, loss of follow-up or patient preference, eventually 11 out of 174 (6 %) patients with a benign GEC and 121 out of 148 (82 %) patients with a suspicious GEC underwent surgery. Of the resected nodules with a suspicious GEC, only 53 (44 %) were malignant. The authors performed an intention-to-treat analysis with the assumption that thyroidectomy is typically recommended for all patients with indeterminate nodules and determined that Afirma® modified care recommendations in 171 of 339 patients (50 %). However, according to TBSRTC, a cytologic diagnosis of AUS does not mandate surgery, thereby challenging the authors' conclusions that the test modified the clinical decision-making. One must also incorporate other factors that may have led to surgery, such as compressive symptoms, family history, etc., before one can accurately assess the impact a molecular marker makes.

In the second study, Duick and colleagues evaluated the impact of a benign Afirma® test result on the endocrinologist-patient decision to operate of patients with thyroid nodules with indeterminate cytology [56]. This cross-sectional multicenter study involving 51 endocrinologists at 21 different practice sites sponsored by Veracyte demonstrated that a benign Afirma® test result could substantially reduce the percentage of patients managed surgically for an indeterminate thyroid nodule from 74 to 7.6 % [56]. Interestingly, when surgery was performed, hemi-thyroidectomy was performed twice as frequently as thyroidectomy, which is the inverse trend for the past 25 years. However, because majority of indeterminate thyroid nodules with benign Afirma® were managed nonsurgically, there is no data available on final pathology. Because of this, it is not possible to figure out whether nonsurgical management had been chosen appropriately. Although it was concluded that benign Afirma® can significantly reduce surgical management of indeterminate thyroid nodules, a longer follow-up for those patients not operated is warranted to completely evaluate the impact of a benign Afirma® test and to evaluate whether the patient eventually required surgery for other indications at some future date.

Our group performed a retrospective evaluation of 114 patients who presented for surgical consultation and who had already undergone molecular testing (Afirma®, Asuragen®, BRAF, NRAS, and/or RET/PTC translocation) to determine the effect on surgical decision-making [57]. A surgical management algorithm including cytology, presence of symptoms, size of nodule, history, and clinical features was created by consensus of four thyroid surgeons. Postsurgical pathology analysis was used to determine the appropriateness of the surgical decision and the utility of the preoperative molecular test. Of the 114 patients, 87 (72 %) underwent surgery, and of those 87, test results altered surgical management in only 9(8 %) patients. Review of final

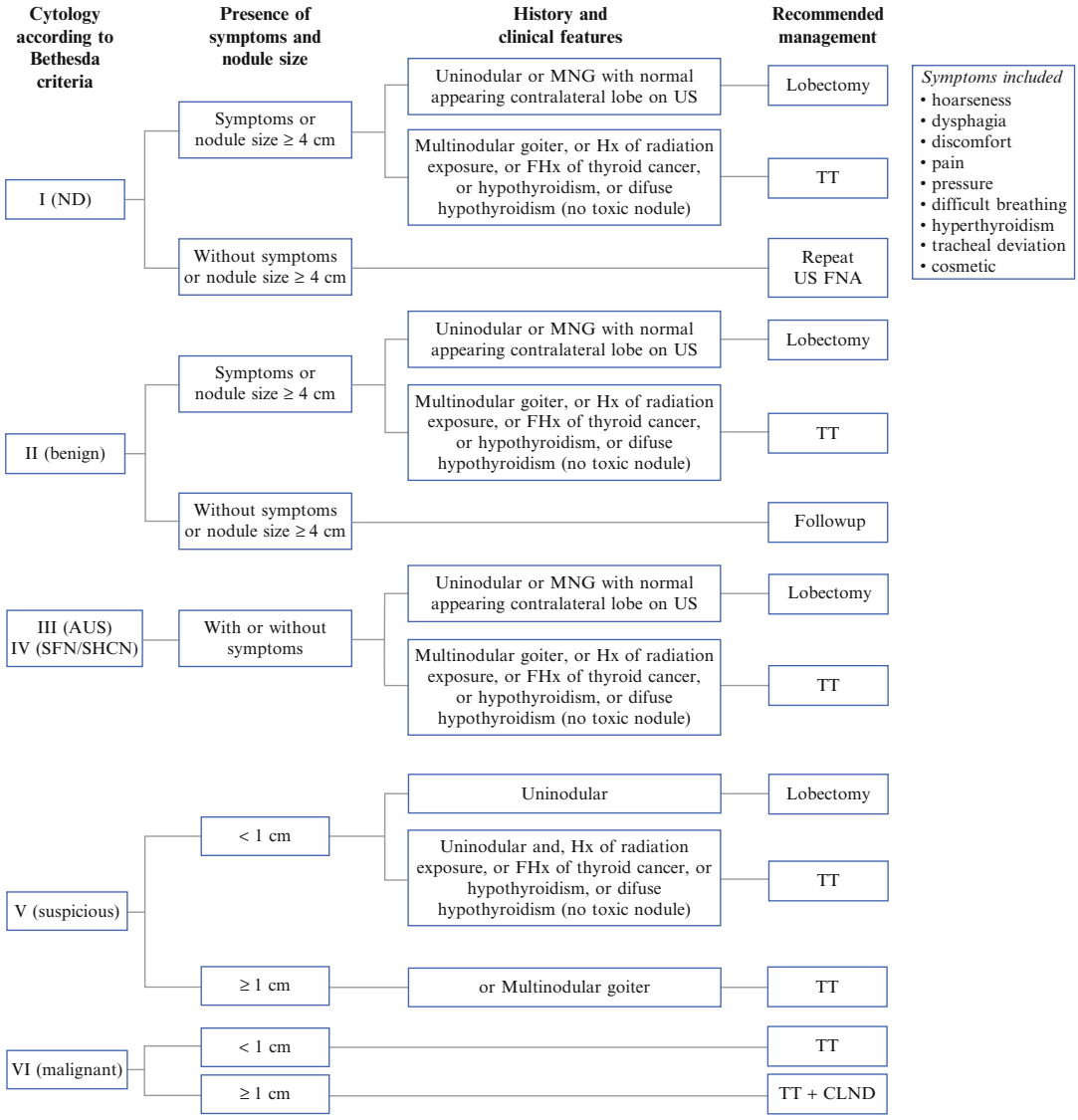

Fig. 11.3 Surgical management algorithm. *FNA* fine-needle aspiration, *AUS* atypia of undetermined significance, *SFN* suspicious for follicular neoplasm, *SHCN* suspicious for Hürthle cell neoplasm, *SFM* suspicious for malignancy, *MNG* multinodular goiter, *US* ultrasound, *Hx* history, *FHx* family history, *TT* total thyroidectomy, *CLND* central lymph node dissection. Reproduced from Han, P.A. (2014) The impact of molecular testing on the surgical management of patients with thyroid nodules. *Annals of Surgical Oncology* 21(6)

pathology demonstrated that molecular testing resulted in appropriate changes in only three (2 %) patients compared to inappropriate changes in six (5 %) patients [57]. This very low proportion of appropriate change in surgical management indicates the overuse of molecular markers and questions their practicality in the management of indeterminate thyroid nodules, particularly in a patient who otherwise would be referred for surgical consultation. It is also concerning that the molecular test resulted in inappropriate surgical management in a greater number of patients. Therefore, the clinical utility of ancillary molecular tests remains yet to be elucidated and done so in the context of a clinical algorithm.

Cost-Effectiveness

The other major concern regarding clinical use of molecular markers is cost-effectiveness. Molecular markers are expensive tests and often not covered by insurance companies. However, their cost could be offset if they can prevent unnecessary surgical interventions and limit diagnostic thyroidectomies. Otherwise, ordering a test that would not alter clinical management would become a financial burden to the patient [25].

Currently available studies on cost-effectiveness of molecular diagnostic markers mostly use hypothetical models to compare costs related to standard of care with and without molecular markers. They suggest that molecular testing for indeterminate cytology may reduce costs mainly because of reduction in either two-stage thyroidectomies for malignant thyroid lesions or unnecessary surgical interventions for benign thyroid lesions [58, 59]. However, with the exception of two studies, none have put them in the context of clinical practice in order to evaluate their true impact, and until this is performed, one cannot assess their efficacy.

Yip and colleagues created decision tree model for a hypothetical group of patients with a 1 cm or larger solitary thyroid nodule [58]. The model was constructed based on the American Thyroid Association (ATA) guidelines with and without molecular testing using the gene expression panel. The authors found that molecular testing decreased the number of diagnostic lobectomies from 11.6 to 9.7 %, and although it caused an additional diagnostic cost of $5031 for every indicated total thyroidectomy ($11,383), the cumulative cost was still less than performing a lobectomy ($7684) followed by a completion thyroidectomy ($11,954).

Li et al. also used decision analysis of a hypothetical group and used a Markov model to evaluate the 5-year cost-effectiveness of routine use of Afirma® in patients with indeterminate nodules [59]. They reported a 74 % reduction in thyroid surgery for benign lesions with no increase in the number of untreated cancers. Based on their model, the median cost of current practice was $1453 more than the practice with a molecular test over 5 years ($12,172 vs. $10,719). Not only was the duration of hypothetical long-term follow-up unclear, but also costs associated with frequent ultrasounds and repeat FNAs were unaccounted for. Patients who would eventually undergo surgery due to either growth of a nodule or development of clinical symptoms were not factored into the observation group.

As such, the main limitation of the above studies is that they are based on analysis of hypothetical patient cohorts and are not prospective. Because of this, they may have not considered the potential role of multiple important clinical factors that significantly impact clinical decision-making used in managing an indeterminate thyroid nodule in the real world. Furthermore, there is no comparison among different molecular markers regarding their cost-effectiveness.

In order to estimate cost-effectiveness of using a diagnostic test, Najafizadeh and colleagues constructed a patient-level simulation model for the diagnosis of thyroid nodules. They measured incremental clinical benefits in terms of quality-adjusted life-years and incremental 10-year costs [60]. They concluded that theoretically a molecular diagnostic test with 95 % sensitivity and specificity should cost less than $1087 per test (including costs of all related procedures such as pathology, physician time, and specimen transport and processing) in order to save quality-adjusted life-years and reduce costs when used as an adjunct to FNA.

To illustrate the existing gap between a commercially available diagnostic test and an ideal test, one can compare Afirma® with the suggested features for a cost-effective diagnostic test: with a sensitivity of 40–52 %, which are significantly lower than the suggested 95 %, Afirma® costs more than $3350, which is then three times more expensive than a cost-effective test.

Therefore, currently available molecular markers should target a significantly higher diagnostic power along with a lower cost in order to be considered cost-effective.

Table 11.2 Summary of pros and cons of different molecular markers in indeterminate thyroid nodules

Molecular marker	Pros	Cons/limitations	Cost
BRAF	High specificity	Low sensitivity	–
Mutation panel	High specificity	Low sensitivity	$2400–2900
Afirma®	High NPV	Low specificity; unclear how to interpret Hürthle cell-rich lesions	$3350–$4000
NGS	Requires only 5–10 ng DNA	–	–
miRNA	–	No consistent miRNA signature	–

Conclusion

Over the past decade, significant progress has been made in the investigation of several molecular markers to further refine the diagnostic role of FNA biopsy and improve the accuracy of preoperative diagnosis of indeterminate thyroid lesions. However, because of the complexity of surgical decision-making processes, the clinical utility and impact of these markers remain unclear. A summary of pros and cons of some of the available molecular markers is presented in Table 11.2.

Larger prospective comparative studies are still needed to address these questions to determine the optimal molecular test(s) and to identify the exact clinical scenarios in which they will both make a difference clinically and be cost-effective.

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Controversies in the Surgical Management of Medullary Thyroid Carcinoma

12

Victoria M. Gershuni, Jennifer Yu, and Jeffrey F. Moley

Introduction

Medullary thyroid carcinoma (MTC) is an uncommon (5 % of all thyroid cancers), often indolent tumor that arises from the neural crest, specifically the calcitonin (CTN)-secreting parafollicular C-cells. While C-cells are located throughout the thyroid gland, they are most prevalent in the upper poles of the thyroid where the majority of MTCs are found. C-cells are known to secrete several neuroendocrine peptides including calcitonin and carcinoembryonic antigen (CEA); calcitonin level is a biomarker that is useful for determining the extent of disease and for detection of recurrence and progression after treatment [1, 2]. CEA can also be used to indicate advanced stage, extent of lymph node involvement, and evidence of distant metastases [3].

The majority of cases of MTC (75 %) are sporadic. Hereditary MTC occurs in the multiple endocrine neoplasia (MEN) type 2A and 2B syndromes that affect approximately 1 in 30,000 individuals [4–6]. This is a uniquely high percentage of patients presenting with a familial predisposition. The diagnosis of MTC warrants referral to genetic counseling.

MTCs in familial cases are usually multifocal and bilateral, whereas sporadic MTC tends to be unilateral. While sporadic MTC most often presents as a palpable thyroid mass or cervical lymph nodes, elevated calcitonin levels may be the first indication of MTC in patients with nodular thyroid disease. Patients may also present with distant metastases or with diarrhea and flushing secondary to secretory products of the MTC tumor cells. In patients with palpable disease, MTC frequently has already metastasized to regional lymph nodes by the time of presentation. In this patient group, the frequency of nodal metastases is reported to be upwards of 50 % [7, 8].

When compared to differentiated thyroid cancer, MTC is somewhat more aggressive. MTC does not respond to radioactive iodine treatment or thyroid suppression. Multiple studies have reported 10-year survival rates between 69 % and 89 % [9, 10].

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Hereditary MTC

The familial syndromes associated with MTC include multiple endocrine neoplasia type 2 (MEN2A and MEN2B) and the related familial MTC (FMTC). In addition to MTC, the clinical features of MEN2A include pheochromocytoma (PHEO), hyperparathyroidism (HPTH), cutaneous lichen amyloidosis (CLA), and Hirschsprung's disease [11]. FMTC is defined as MTC without any other endocrinopathies and is considered to be a clinical variant of MEN2A. Thus, MEN2A has been divided into four clinical variants: classical MEN2A (MTC accompanied by PHEO and/or HPTH), MEN2A with Hirschsprung's disease, MEN2A with CLA, and FMTC. MEN2B is characterized by development of MTC at an extremely young age, sometimes in infancy. The MEN2B phenotype may include PHEO; mucosal neuromas of the lips, tongue, GI tract, and conjunctiva; and variable development of megacolon, skeletal abnormalities, and markedly enlarged peripheral nerves [12]. MEN2 syndromes are secondary to germline activating missense mutations in the REarranged during Transfection (*RET*) proto-oncogene which codes for a transmembrane receptor tyrosine kinase (Fig. 12.1). All of these syndromes report almost complete penetrance of MTC, which presents at an earlier age than sporadic cases and is most often multifocal and bilateral. The various other clinical features of MEN2 have differing penetrance, and the presentation is dependent on the specific syndrome and mutation [13]. Hereditary MTC follows the transformation of C-cell hyperplasia, with an age-related progression to cancer [14]. Multicentric C-cell hyperplasia (CCH) is recognized to be an intermediate, premalignant transformation from normal C-cells to microscopic MTC and eventually macroscopic disease [14, 15]. CCH represents a precursor lesion along a stepwise progression to malignancy [16]. Thus, all patients with evidence of CCH should undergo genetic testing to exclude the presence of *RET* mutations. The estimated time for progression from CCH to overt MTC is 2–5 years depending on the *RET* mutation. Carriers of an extracellular domain mutation (codons 609, 611, 618, 620, 630, and 634) progress at a much faster rate than carriers with an intracellular domain mutation (codons 768, 790, 791, 804, and 891) [17, 18].

Genetics

The activating gene mutations responsible for MTC were first identified in 1993 and were found to affect the *RET* proto-oncogene on chromosome 10q11.2 [19, 20]. An autosomal dominant germline mutation in this gene is found in virtually all patients with hereditary MTCs and in approximately 5–10 % of apparently sporadic MTCs [21, 22]. There has been controversy over whether it is necessary to perform genetic testing on individuals with apparent sporadic MTC (no family history, unilateral tumors). Recent opinion is reflected in the American Thyroid Association (ATA) guidelines for MTC which recommend germline *RET* testing with genetic counseling for all patients with CCH or MTC [11, 23].

Specific genotype–phenotype relationships are characteristic in the hereditary MTC syndromes. These are important to understand to direct management. MEN2A and the variant FMTC are most frequently due to mutations in codons 609, 611, 618, and 610 in exon 10 and codons 630 or 634 in exon 11 [11, 24]. MEN2B and some FMTC are associated with germline mutations in the intracellular tyrosine kinase domain of the *RET* protein. Greater than 95 % of MEN2B cases are the result of a single point mutation found in codon 918 (exon 16, p. M918T). In sporadic MTC, somatic *RET* mutations are found 6–9.5 % of the time and most commonly are detected in codon 918. The 2009 ATA categories for hereditary MTC used A–D classifications to specify risk of MTC (age of onset and aggressiveness). In the 2015 guidelines, the level D category is changed to a new category, "highest risk" (HST), that includes patients with MEN2B and the *RET* codon M918T mutation. The 2009 level C category is changed to a new category, "high risk" (H), that includes patients with MEN2A and *RET* codon C634 mutations. The 2009 level A and B categories are combined into a new category "moderate risk"

Codon	Risk Level	MEN 2B	MEN2A			FMTC	HSCR
			MTC	Pheo	HPT		
533	I		X	X		X	
9-bp ins	I*					X	
608	I*		X				
609	II*		X	X	X	X	X
611	II		X	X	X	X	X
618	II		X	X	X	X	X
620	II		X	X		X	X
630	II*		X		X	X	
631	I*		X	X		X	
634	II		X	X	X	X	
768	I		X	X		X	
777	I*					X	
790	I		X	X		X	
791	I		X	X	X	X	
804	I		X	X	X	X	
804 +806	III*	X					
883	III	X					
891	I		X	X		X	
812	I*					X	
918	III	X					

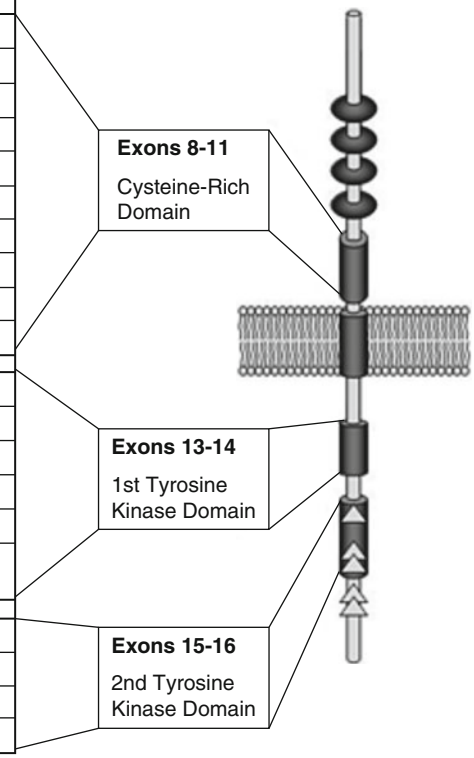

Fig. 12.1 Genotype–phenotype correlations in MEN2A and MEN2B

(MOD) that includes patients with hereditary MTC and *RET* codon mutations other than M918T and C634. This classification is important in determining appropriate age of preventative thyroidectomy and age of screening for pheochromocytoma. The previously designated FMTC is now considered a variant of MEN2A [23].

Prophylactic Thyroidectomy in Patients with Hereditary Disease

Patients with hereditary MTC benefit from preventative surgery, in which the organ at risk for cancer—the thyroid—is removed before cancer develops or spreads beyond the confines of the gland. Knowing the particular germline *RET* mutation allows prediction of the age of onset of the phenotype, and preventative surgery may be performed before development of local spread or metastatic disease [25]. It is probable that timely removal of the thyroid gland significantly reduces morbidity and mortality. However, even with early thyroidectomy, the surgery is not always prophylactic, as children with aggressive mutations will have already developed CCH and/or microscopic MTC by the time of operation. Early surgery is not without risk and remains controversial despite curative potential due to the belief that the rate of complications and risk increases with the technical difficulty of pediatric thyroidectomy. The surgeon should be able to appropriately identify the superior and recurrent laryngeal nerves as well as the four parathyroid glands. Likewise, in cases of neck metastases, surgical expertise is extremely important to ensure adequate central and lateral neck dissection. Another concern is ensuring adequate thyroid hormone replacement in the pediatric population; not

replacing appropriately can lead to significant damage and inadequate brain development in very young children as compared to older children and adults. Notwithstanding, complications are significantly minimized when a highly skilled, expert surgeon performs the operation. Surgeons with experience in pediatric thyroidectomy see no technical benefit in delaying thyroidectomy beyond 5 years old [26]. When performing total thyroidectomy with possible central compartment dissection in the pediatric population, particular attention must be dedicated to the parathyroid glands. In small children and infants, the parathyroids are extremely small and often translucent making them difficult to distinguish from the surrounding tissues and making the dissection particularly painstaking.

When preventative (or prophylactic) thyroidectomies in children with *RET* mutations were first reported in the 1990s, most American surgeons recommended thyroidectomy before age five in MEN2A and before 1 year of age in MENB patients [27, 28]. Some European groups, however, advocated waiting until the calcitonin level was elevated to perform thyroidectomy. At present, consensus is close, as reflected in the 2015 ATA guidelines [23]. These recommendations are based upon consensus opinion of a group of North American and European experts including the senior author of this chapter (Jeffrey F. Moley). These guidelines state that, first of all, only experienced thyroid and parathyroid surgeons in tertiary care centers should be responsible for the management of children with MEN2A or MEN2B. Secondly, children in the ATA–HST category (see above) with a *RET* codon M918T mutation (MEN2B) should have a thyroidectomy in the first year of life, perhaps even in the first months of life. In the absence of suspicious lymph nodes, the performance of a central neck dissection (CND) should be based on whether the parathyroid glands can be identified and left in situ or autotransplanted. Thirdly, children in the ATA–H category (see above) should have a thyroidectomy performed at age 5 years or earlier based on the detection of elevated serum calcitonin levels. A CND should be performed in children with serum calcitonin levels above 40 pg/ml or with evidence on imaging or direct observation of lymph node metastases. The European surgeons felt that the threshold for CND should be a calcitonin level of 20 pg/ml [29]. Lastly, the new ATA guidelines state that children in the ATA–MOD category (see above) should have a physical examination, US of the neck, and measurement of serum calcitonin levels beginning around 5 years of age. The timing of thyroidectomy should be based on the detection of an elevated serum calcitonin level; however, 6-month or annual evaluations may extend to several years or decades. Parents who are concerned about a long-term evaluation program may opt to have their child's thyroid gland removed around 5 years of age. The surgeon and pediatrician caring for the patient, in consultation with the child's parents, should decide the timing of thyroidectomy. These recommendations are summarized in Table 12.1.

Management of the parathyroids in preventative thyroidectomy has been controversial. In our first series [27, 30], all patients had four gland parathyroidectomy with autotransplantation to the nondominant forearm. This resulted in a 6 % incidence of permanent hypoparathyroidism. Since 2003, the senior author has attempted to preserve glands on an intact vascular pedicle with autotransplantation reserved for nonviable glands or glands removed with the central neck lymph nodes. This resulted in a 1 % rate of hypoparathyroidism [31]. This strategy is similar to what other groups have reported [28, 32, 33] and is the approach recommended in the ATA guidelines [23].

In the early days of preventative thyroidectomy, our group routinely performed CND with the thyroidectomy. There were no recurrent laryngeal nerve injuries, but the routine performance of CND may have contributed to the 6 % rate of hypoparathyroidism we reported [30]. The rate of central neck (level VI) lymph node metastases is 0 % in patients with basal calcitonin level <20 pg/ml and is extremely low in patients with levels <40 pg/ml [34]. The new guidelines recommend CND in patients with basal calcitonin >40 pg/ml [23].

Management of Patients with Clinically Evident Sporadic and Hereditary MTC

The majority (75 %) of MTC cases are sporadic and occur between the fourth and sixth decade [11]. The most common presentation for sporadic MTC and index cases of hereditary MTC is a palpable neck mass, either a solitary thyroid nodule or, in 35–50 % of cases, an enlarged cervical lymph node [8]. By this time, cervical lymph node metastases are present in 70 % of cases, and 10–15 % of patients also have distant metastases [8, 35]. Metastases develop via lymphatic spread to the central compartment of the neck (levels VI and VII), then to the ipsilateral jugular nodes (levels II–V), followed by the contralateral cervical nodes (Fig. 12.2) [36]. Often, the presenting mass itself turns out to be a metastatic lymph node. Neck ultrasound should be integrated into the initial diagnostic workup to fully evaluate thyroid tumors and neck lymphadenopathy (Fig. 12.3) [37]. The most common sites for distant metastases in MTC are the upper and anterior mediastinum, liver, lungs, and bone. Contrast-enhanced CT of the chest, mediastinum, and abdomen should also be employed during initial diagnosis of MTC and as part of the metastatic workup. On imaging, distant metastases can appear large and calcified or may be present in a miliary pattern as small micrometastases that are not discernable by CT. The American Joint Committee on Cancer (AJCC) TNM (tumor, node, metastasis) classification system calculates 10-year survival rates for stages I, II, III, and IV MTC at 100 %, 93 %, 71 %, and 21 %, respectively [38, 39].

Table 12.1 Recommendations for patients with hereditary disease

Risk category	Patient population	Management
ATA–HST	MEN2B *RET* codon M918T mutation	Thyroidectomy ± central neck dissection within the first year of life
ATA–H	MEN2A *RET* codon C634 mutations	Thyroidectomy ± central neck dissection[a] at age 5 years or earlier
ATA–MOD	Hereditary MTC *RET* codon mutations other than M918T and C634	Annual physical exam, neck ultrasound, serum calcitonin measurement beginning at age 5 years

HST highest risk, *H* high risk, *MOD* moderate risk, *MEN* multiple endocrine neoplasia, *MTC* medullary thyroid cancer

[a]Central neck dissection should be performed for serum calcitonin levels >40 pg/ml or for clinical/radiologic detection of lymph node metastases

Symptomatic thyroid masses are present in 15 % of patients, and due to their posterior location, often cause compressive symptoms including dysphagia, hoarseness, shortness of breath, and coughing (Fig. 12.4). If the recurrent laryngeal nerve is involved, laryngoscopy during workup can reveal vocal cord dysfunction. Additionally, flushing, diarrhea, and/or weight loss can be a presenting sign in patients with high calcitonin levels. In patients with MEN2, the presenting symptoms may be due to pheochromocytoma (palpitations, headaches, or sweating) or hyperparathyroidism (bone pain, kidney stones, or fatigue).

Sporadic MTC does not follow a predictable course; some are aggressive and invasive, and others are slow growing and indolent. Some patients with long calcitonin doubling times may live a long time even with distant metastases [11, 40, 41]. Postoperatively, patients with normal basal serum CTN levels are considered to be "biochemically cured" with a 10-year survival upwards of 97.9 % [42].

Preoperative Evaluation

Upon initial workup of newly diagnosed MTC, the thyroid mass should be assessed for its size and relation to adjacent structures. MTC can invade into local structures by extending through the posterior thyroid capsule or into the trachea, the jugular vein, or the recurrent laryngeal nerve. The fast rate of spread via lymphatics warrants particular attention to the cervical area including the central neck compartment (levels VI and VII nodes) and the lateral compartments (levels II to

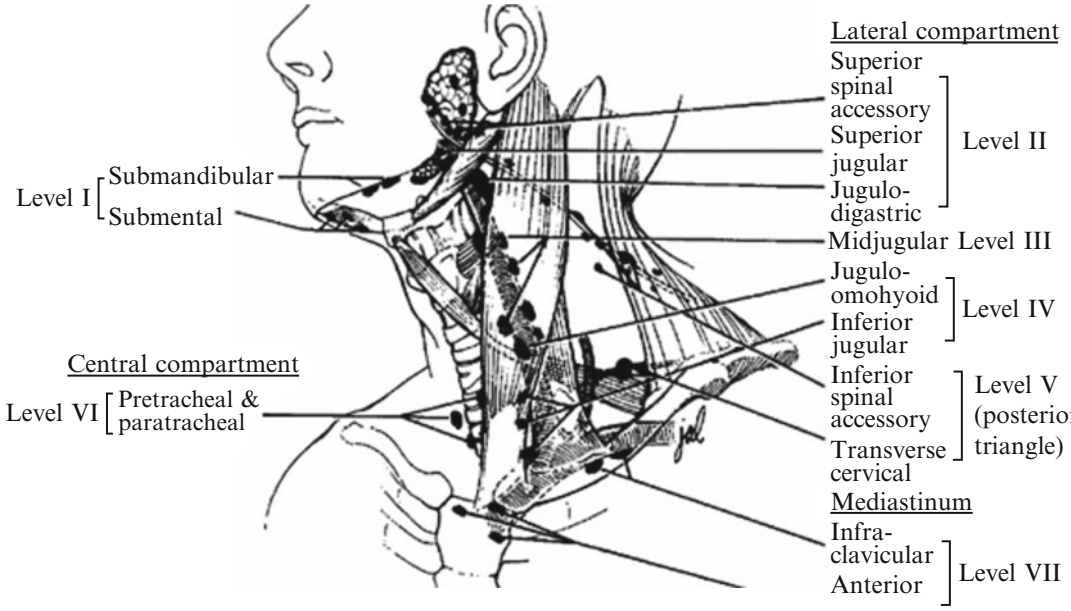

Fig. 12.2 Diagram showing lymph node groups in the neck (reprinted with permission from Musholt, T. J. and J. F. Moley (1997). "Management of Persistent or Recurrent Medullary Thyroid Carcinoma." *Problems in General Surgery* 14(4): 89–109)

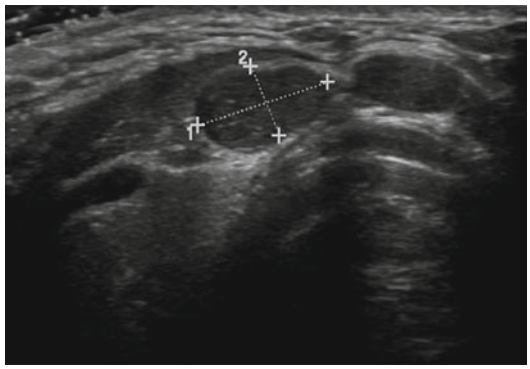

Fig. 12.3 Ultrasound appearance of metastatic medullary thyroid carcinoma nodal metastasis

V, bilaterally). Pathological exam of fine needle aspirate (FNA) specimens will reveal characteristic stromal amyloid in the absence of thyroid follicles. However, FNA is only 50–80 % accurate, but immunohistochemical staining for calcitonin and/or CEA can improve the accuracy. Additionally, preoperative calcitonin levels can be helpful in both diagnosing and staging MTC [34, 43, 44]. Basal calcitonin levels have been correlated to the presence of nodal metastases and distant metastases (>150 pg/ml, and often >1000 pg/ml). In over 50 % of patients with MTC, CEA serves as another useful tumor marker with levels >30 ng/ml indicative of a poor prognosis and levels >100 ng/ml pointing to extensive lymph node involvement and distant metastasis [34]. Genetic testing should be performed on kindreds of all newly diagnosed *RET* mutation carriers, starting with first-degree relatives.

Surgical Approach to Clinically Evident Disease

Due to the unique etiology and behavior of MTC, the standard treatment for newly diagnosed MTC requires surgical removal of the thyroid with regional lymph node dissection. Total thyroidectomy represents the only curative option for MTC due to the lack of curative systemic chemotherapy, radiation, or thyroid suppression. MTC is often multifocal with evidence of microcarcinoma throughout the gland and is accompanied by a high frequency of nodal metastases, which together influence the need for surgical manage-

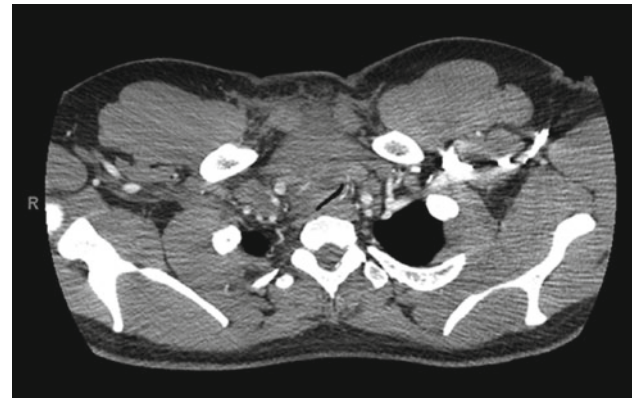

Fig. 12.4 Computerized tomographic image of locally advanced medullary thyroid cancer with significant tracheal compromise

ment as the only potentially curative treatment. In patients with palpable disease, nodal metastases are already present in more than 70 % of patients [7, 35]. Biochemical markers such as basal and stimulated calcitonin levels serve as a surrogate for C-cell mass and allow the surgeon to assess the adequacy of extirpation.

Following diagnosis of confirmed sporadic or hereditary MTC, ultrasound of the neck, focusing on lymph nodes, should be done, and serum levels of CTN and CEA should be obtained. Additionally, for patients with hereditary MTC, the presence of pheochromocytoma or hyperparathyroidism should be evaluated prior to surgery.

Based on a study of 300 consecutive patients with MTC undergoing compartment-oriented surgery, risk for lymph node metastases in ipsilateral central and lateral neck, contralateral central neck, contralateral lateral neck, and upper mediastinum corresponded with preoperative serum CTN levels greater than 20 pg/ml, 50 pg/ml, 200 pg/ml, and 500 pg/ml, respectively. Further, levels over 1000 pg/ml necessitate bilateral compartment-oriented neck dissection in order to achieve biochemical cure [34].

Patients with no evidence of local invasion or lymph node metastases (basal calcitonin <40 pg/ml) should undergo total thyroidectomy. If the basal calcitonin is >40 pg/ml but <150, CND and ipsilateral level 2–4 neck dissection should be considered even if ultrasound imaging is negative. If the basal calcitonin is >200, dissection of the contralateral neck should be considered [11, 23]. While sporadic MTC tends to be unilateral, the frequency of bilateral MTC in these patients remains controversial and has been found in 0–9 % of patients without a germline *RET* mutation [45–47], so the ATA recommendation is for total thyroidectomy in these patients as well. This operation incorporates removal of all nodal tissue between the carotids bilaterally and between the hyoid bone superiorly and the innominate vein inferiorly (Fig. 12.5) [8, 48–50]. When assessing compartment-oriented dissection, Dralle et al. reported improved recurrence and survival rates when using a systematic compartment-based approach to the removal of all nodal tissue in the central neck compared to "berry picking" procedures that only removed grossly involved nodes [48]. Greater than 70 % of patients with palpable MTC at presentation—regardless of mutation carrier status—harbor cervical lymph node metastases. These patients have a similar rate of unilateral nodal disease with spread to ipsilateral jugular nodes (levels II–V) and a fairly high rate of contralateral jugular nodal disease as well [8]. In this patient population, lymph node disease is often undetected preoperatively or even during assessment intraoperatively. Weber et al. looked at 36 patients undergoing treatment of MTC by total thyroidectomy with central and lateral neck dissection and found lymph node metastases in 75 % of patients [51]. Dissection of lateral compartment (levels II–V) lymph nodes depends on preoperative US findings, biochemical markers (CTN and CEA), and intraoperative findings. Thus, at a minimum, total thyroidectomy with

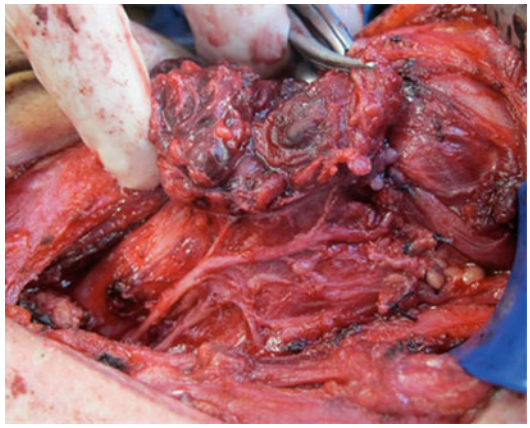

Fig. 12.5 Intraoperative photograph of thyroidectomy/central neck dissection for multifocal medullary thyroid carcinoma

Table 12.2 Indications for neck dissection

Clinical characteristics	Recommendations
No clinical evidence of lymph node disease	
Basal serum calcitonin >40 pg/ml or palpable primary tumor	Central neck + ipsilateral level II–V dissection
Basal serum calcitonin >200 pg/ml	Central neck + bilateral level II–V dissection
Palpable lymphadenopathy	Central neck + bilateral level II–V dissection

central lymph node dissection and unilateral dissection of jugular (level II–V) nodes should be performed in all newly diagnosed cases of palpable MTC. To determine the extent of surgery, preoperative ultrasound imaging can help identify metastatic nodes [37]. Extensive lymph node disease on exam or preoperative imaging studies revealing bilateral involvement warrants bilateral neck dissection of levels II–V [8, 34]. However, it is important to note that the sensitivity of the surgeon's intraoperative assessment for nodal metastases was reported as 64 % with a specificity of 71 % [8]. Recommendations for neck dissection are summarized in Table 12.2.

Management of the Parathyroids

While most surgeons prefer to leave the parathyroid glands in situ when possible, if there is any evidence of devascularization or compromise of the vascular pedicle, it is recommended to remove and autotransplant the gland to the sternocleidomastoid (SCM) or forearm muscles [52]. Due to the intimate relation of the parathyroid vasculature, thyroid lymphatics, and the posterior capsule of the thyroid, it is often impossible to remove all thyroid tissue with central nodes and ensure viable parathyroids. Therefore, parathyroidectomy with autotransplantation should be done for any and all compromised parathyroids [31]. As described in the literature, the parathyroid glands are removed and placed in cold saline. The glands are prepared for autotransplantation to either the SCM or forearm by slicing the glands into 1- to 3-mm fragments. Groups of two to three fragments of parathyroid tissue are autotransplanted into individual muscle pockets [53, 54]. The SCM is preferred for those with sporadic MTC, FMTC, or MEN2B. For patients with hyperparathyroidism at the time of operation or with MEN2A and a high genetic predisposition, the forearm is the preferred site for autotransplantation due to ease of access should excision be necessary in the future. Postoperatively, patients should receive calcium and vitamin D supplementation for approximately 4–8 weeks, at which point the autografts will take over [30].

Postoperative Surveillance

Following total thyroidectomy, thyroid hormone replacement is required for life. In patients who undergo parathyroidectomy with autotransplantation, calcium and vitamin D supplementation will be required for 4–8 weeks postoperatively until the autografts are fully functioning and able to take over calcium regulation. Monitoring for adequacy of the resection, persistent disease, or recurrence is achieved with serial CTN levels. Immediately following the operation, CTN levels may be falsely elevated or unreliable. Levels should stabilize after approximately 72 h, but in some patients it may be weeks to months until they have normalized. Some investigators suggest that 3 months may be a more optimal interval for post-op follow-up [55]. Patients whose CTN levels drop to normal values (<5 pg/

ml) are considered to have achieved "biochemical cure." Complete post-op normalization is associated with decreased long-term risk of MTC recurrence. However, this benefit is less clear for long-term survival [42, 56]. In a study of 1453 patients, 400 were considered to have achieved "biochemical cure" at 6 months status post total thyroidectomy for MTC; of these, 15 (3.7 %) ultimately developed recurrent MTC discovered with stimulated serum CTN levels [57].

Oncologic Follow-Up

In general, to determine whether the operation was curative, all patients status post total thyroidectomy and central compartment resection should have CTN levels drawn two weeks postoperatively and annually thereafter. Persistent or recurrent MTC can be determined by a persistent or recurrent elevation in CTN; these patients should have further investigation by imaging. However, due to the indolent nature of MTC, biochemical evidence of disease may indicate micrometastases, which will not be evident on imaging until much later. Post-op CTN elevations of less than 150 pg/ml after total thyroidectomy indicate evidence of locoregional disease and do not exclude distant metastases. When recurrent disease is found localized to the neck, reoperation should be considered to manage and remove all remaining disease. Confirmation of metastatic MTC can be achieved with fine-needle aspiration biopsy; CTN levels in the FNA washout fluid can enhance the specificity and sensitivity of the procedure [58]. Locoregional control of the disease may result in long-term survival benefit and prevent complications of recurrence in the neck [50].

Following prophylactic thyroidectomy in *RET* mutation carriers, the data is limited regarding long-term risk of recurrence or metastases in those with normal preoperative CTN levels. In these patients, thyroidectomy is likely curative, and serial CTN levels should be measured annually for ongoing monitoring.

Postoperatively, the ATA recommends utilization of the TNM classification system for staging, number of lymph node metastases, postoperative serum CTN level, and CTN and CEA doubling times to predict outcomes and plan long-term management.

Management of Persistent or Recurrent Disease

In patients with MEN2A or FMTC fortunate enough to have prophylactic operations following genetic testing or detection of an elevated CTN level, thyroidectomy is likely curative [30, 31, 59]. However, in those who present with a palpable tumor, greater than 50 % will have persistent disease after surgery, which is indicated by persistent CTN elevations [60, 61]. Persistent MTC often follows an indolent course; many patients do well postoperatively for many years [62]. However, other studies have indicated a poor outcome in these patients [63, 64]. In patients with persistently high CTN, imaging studies or physical exam may reveal nodal metastases for which further surgical removal and/or formal functional neck dissection should be performed. If the previous surgery did not include nodal clearance, reoperation can decrease disease burden. However, if the previous thyroidectomy was accompanied by adequate central and lateral node dissection, reoperation should not be pursued unless disease is detectable on imaging [50]. Following reoperation, multiple groups have reported a significant reduction in stimulated calcitonin levels with some patients attaining normalization [49, 65–67].

For patients with recurrent or persistent disease localized to the neck and without evidence of distant metastases, repeat operation of the central and lateral compartments can yield up to 50 lymph nodes for evaluation. Full extirpation provides the possibility of surgical cure in MTC unless there are more than 10 lymph node metastases identified, which is considered the surgical "window of opportunity" for cure. As mentioned earlier, due to the nature of thyroid C-cells lacking iodine transporters, MTC is not responsive to radioactive iodine, and postoperative radioactive iodine is not indicated.

Patients with CTN levels greater than 150 pg/ml are at risk for distant metastases [34]. At levels of 5000 pg/ml or greater, the chance of distant metastases exceeds 50 % and approaches 100 % with CTN levels over 20,000 pg/ml. Metastatic MTC often is undetectable on CT imaging due to its miliary appearance. Detection of persistent or recurrent disease can be enhanced with use of multiple imaging modalities including, but not limited to, neck and chest CT scan, liver three-phase contrast-enhanced CT scan, or contrast-enhanced MRI. In cases where metastases are not seen on imaging, multiple small (1–3 mm) foci of MTC may appear as white raised nodules on the liver surface only visible on laparoscopy [68]. This study highlighted the lack of sensitivity (7 %) and false-negative rate (20 %) of conventional imaging when looking for visceral metastases in MTC. However, it is important to consider several factors when evaluating for distant metastases. It is unclear whether there is benefit of immediate intervention in asymptomatic and stable patients with distant metastases. In most cases, observation alone is adequate.

Systemic therapy is now available and FDA-approved for metastatic MTC [69–71]. These drugs have a response rate of less than 50 %, duration of response of 1–2 years, and significant side effects. For these reasons, systemic therapy is not recommended for MTC patients unless they have rapidly progressive metastatic disease or are showing signs of failure to thrive due to the malignant burden [11, 23, 72, 73].

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Central Lymph Node Dissection for Well-Differentiated Cancer

13

Allan Siperstein

Introduction

The goal of any operation for well-differentiated thyroid cancer is to provide the best oncologic outcome, individualized to the patient, but avoid the morbidity of excessively radical procedures. Historically, well-differentiated thyroid cancer was treated with the same extent of nodal dissection as was done for squamous cell carcinoma of the head and neck, namely, a radical neck dissection. With the realization that thyroid metastatic disease tends to be less infiltrative, as well as the use of radioiodine ablation, less radical procedures are now performed. There is widespread agreement that jugular nodal disease only requires resection if clinically involved. Clinically involved central neck lymph nodes also require removal. A major area of controversy is whether prophylactic central neck dissection is required for thyroid cancer of follicular cell origin. The exact definition of a prophylactic versus a therapeutic neck dissection varies. When neck dissection is performed, there is varied practice in terms of how thoroughly the central compartment is cleared of its nodal burden. There is also controversy as to whether a unilateral versus a bilateral central neck dissection should be performed. How to interpret or act on the final pathologic findings is also an area of controversy. Although any nodal involvement is staged as N1 disease, biologically the findings of microscopic nodal involvement are clearly different than that of nodal replacement or extranodal extension. In terms of gaining a better perspective into any of these areas, it is important to understand that with well-differentiated thyroid cancer, although this may impact the recurrence rate in the neck, given the excellent long-term survival, mortality is unlikely to be affected.

Understanding the Biology of Thyroid Cancer

The classic understanding of cancer biology as espoused by Sir William Halsted states that there is an inevitable and systematic progression of the disease. The cancer begins as a primary lesion and then grows and invades surrounding tissues. Following this, there are metastases to regional lymph nodes or to distant sites. This theory that the tumor cells progress like an invading army led to the conduct of radical procedures in the hopes that resecting beyond the area of tumor progression would lead to cure. This was the basis for the Halsted radical mastectomy. With a more modern understanding of tumor biology,

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far less radical operations could be performed with equal survival rates and far less morbidity and disfigurement. When operations as minimalist as lumpectomy for breast cancer were initially proposed, this created much controversy as it went against not only the dogma of the day but the current accepted theory of cancer biology.

Thyroid cancer has undergone a similar evolution in both the radicality of the surgical procedure and a more modern understanding of tumor biology. Classically, a total thyroidectomy with the disfiguring radical neck dissection was routinely performed. This mimicked the extent of nodal surgery performed for the more invasive squamous cell carcinoma of the head and neck. With the realization that thyroid cancer spread to the jugular nodes a minority of the time and that extranodal extension was not frequent, surgical practice evolved such that a modified neck dissection, with sparing of the sternocleidomastoid muscle and jugular vein, was performed only therapeutically when nodes were involved.

The biology and, hence, staging of well-differentiated thyroid cancer differ from many other neoplasms in that nodal involvement is relatively common, but does not have great impact on survival (stage 2 disease). Extra thyroidal extension of the primary tumor, however, portends a much worse biology of disease (stage 3). More recent studies looking at the presence of circulating thyroid cells in the periphery have demonstrated that a majority of thyroid cancers shed cells into the circulation, even early in their development. This is been demonstrated for many other types of tumor as well. The implication is that from a biologic point of view, thyroid cancer is a systemic disease, even if the primary lesion appears to be grossly well contained. Once the primary lesion has been excised, these circulating cells disappear with several hours [1]. The biology of thyroid cancer, and probably many other tumors as well, points to the fact that although systemic from an early time, adverse behavior is dictated by those cells' ability to settle and proliferate in their remote environment.

Great advances have been made recently in understanding the mutations responsible for the development of thyroid cancer. Key to directing patient-specific therapies will be the understanding of how specific genetic mutations affect the biology of thyroid tumors. Some attempts have been made in this area, with the early suggestion that BRAF mutations conferred a more aggressive behavior and thus may warrant more radical surgery. In subsequent studies, using multivariate analysis to control for known pathologic findings at the time of surgery has failed to demonstrate that BRAF-positive tumors behave any more aggressively [2].

Prophylactic Neck Dissection: Background and Definition

Whether to perform a prophylactic total thyroidectomy in a patient with well-differentiated thyroid cancer remains a major area of controversy. This is by no means a new topic of discussion. In 1955 George Crile Jr. published a paper on the more conservative procedures that he had been performing [3]. He specifically studied patients who had not undergone prophylactic central neck dissection. He concluded: "Despite the fact that lymph nodes were not removed prophylactically when they were not grossly involved, in only 1 of the 27 patients who had no evidence of involvement of nodes at our original operation was there subsequent development of recognizable metastases to cervical nodes. This recurrence was effectively corrected by removal of the involved group of nodes."

The difference between a therapeutic and prophylactic neck dissection is not always clearly distinguished in the literature. In a broad sense, a therapeutic dissection is done for known metastatic disease, whereas a prophylactic dissection is done in the absence of demonstrable disease. Often not clearly specified, however, is when this distinction is made in the course of the patient evaluation, the modalities used to determine nodal disease, and the extent to which the nodes are involved:

- A patient having a preoperative neck ultrasound that demonstrates enlarged central neck lymph nodes and a subsequent fine needle aspiration confirming metastatic papillary thyroid cancer would clearly meet any definition of a therapeutic neck dissection.

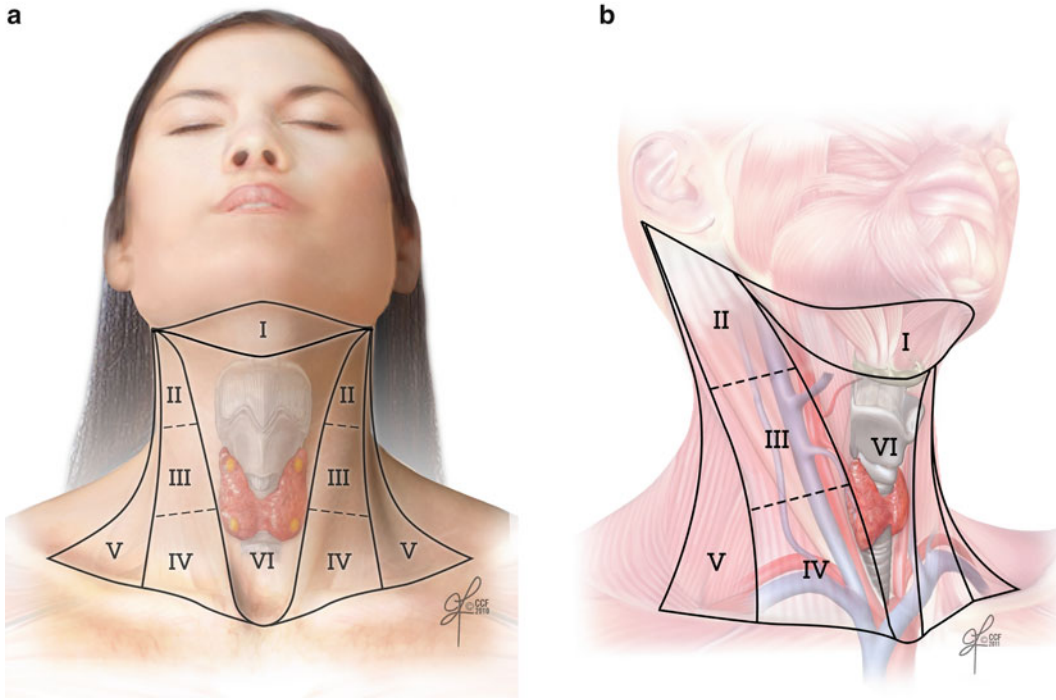

Fig. 13.1 (**a**) Anterior and (**b**) oblique views of the neck demonstrating the anatomic compartments. Level VI corresponds to the central neck compartment and is further subdivided into *left* and *right sides*. Reprinted with permission, Cleveland Clinic Center for Medical Art & Photography © 2011–2015. All Rights Reserved

- If a patient's preoperative ultrasound showed no enlarged nodes, however at surgery several mildly enlarged nodes where excised and demonstrated to have metastatic tumor (a lymph node sampling), this finding may prompt a formal therapeutic node dissection. Some papers consider this prophylactic or fail to define this specific situation.
- A less clear situation arises if the preoperative neck ultrasound is unrevealing and at surgery no enlarged nodes are identified. If central neck lymph nodes are sampled and reveal (typically microscopic) tumor, then technically formal central neck dissection would be considered therapeutic.
- If a patient has no enlarged nodes identified or at the time of surgery and then undergoes central neck dissection, then this would be the purest definition of a prophylactic central neck dissection.

There is also the variability in the literature as to what constitutes a central neck dissection. This has been well addressed in the American Thyroid Association guidelines [4] (Fig. 13.1). The boundaries of a central (level VI) nodal dissection involve removing all of the nodal and fibrofatty tissue between the following boundaries: superiorly the upper border of the cricoid muscle, inferiorly the innominate artery, laterally the carotid artery, and medially the contralateral edge of the trachea. This typically requires skeletonization of the recurrent laryngeal nerve, in particular to excise those nodes that lay posterior and medial to the nerve. If not initially resected, at reoperation this represents a particular challenge and risk to nerve integrity. Also in the course of this dissection, the inferior parathyroid is unlikely to be preserved on its native vasculature and typically requires autotransplantation. It is recommended that a biopsy of a small portion of the parathyroid

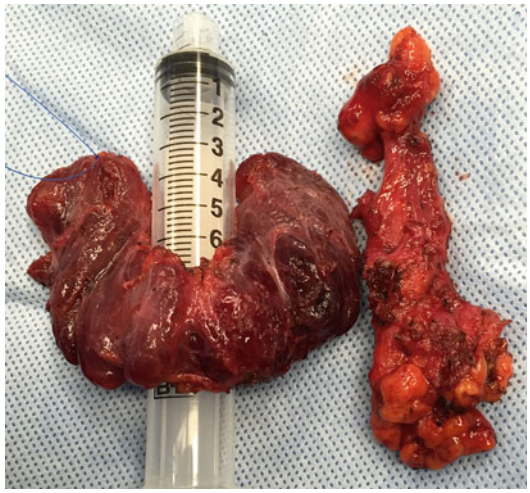

Fig. 13.2 Photograph of total thyroidectomy specimen with *left central neck* contents after thorough dissection

be sent for frozen section to confirm correct identification prior to autotransplantation. In some situations with matted nodes, the parathyroid may not be able to be identified or require sacrifice for fear of autotransplanting tumor. The upper parathyroid gland is usually able to be preserved in situ; however, autotransplantation may be required as well. Although the exact technique of autotransplantation varies, this is typically done by mincing the gland into 1 mm cubes and then auto transplanting into separate pockets in the sternocleidomastoid muscle (Fig. 13.2).

A lesser extent of nodal dissection may also be incorrectly labeled as a central neck dissection. This may involve removal of a cluster of lymph nodes lateral and inferior to the thyroid lobe and in some instances are removed en block with the thyroid. This procedure is better termed a lymph node "sampling." It may provide some staging information but is considered an inferior procedure from an oncologic point of view. Reoperating in the central neck after such a procedure can be challenging, both in terms of recurrent laryngeal nerve and parathyroid preservation, as well as the oncologic completeness of the procedure.

Indications and Outcomes

The key controversy is whether prophylactic central neck dissection is a better operation from a risk-benefit perspective. From a purely oncologic point of view, prophylactic central neck dissection cannot be inferior to a lesser procedure. The key question, obviously, is whether it confers any oncologic advantage and at the expense of what added morbidity. Ideally, a prospective randomized trial could address this question. When the feasibility of this is calculated, however the number of patients needed and the duration of follow-up so lengthy that it would be totally impractical [5].

Numerous studies have investigated various outcomes of prophylactic central neck dissection in an attempt to investigate the question of oncologic superiority. Performing a central neck dissection clearly upstages patients. In a small but well-studied group of patients by Wang at al. [6], unsuspected metastatic nodes were identified in 41 % of patients that resulted in indicating for radioiodine ablation in 33 %. When thyroglobulin was studied, no advantage could be identified given the high proportion of patients with undetectable levels.

The identification of sonographically positive nodes preoperatively has been shown to result in a higher long-term recurrence rate. For those patients who had sonographically negative nodes preoperatively, whether or not nodes were found to be involved at the time of surgery, did not affect long-term recurrence. This would imply that smaller lymph nodes that are not able to be identified sonographically have a little adverse oncologic consequence [7].

This potential for oncologic superiority has to be balanced with the potential for an increased risk of hypoparathyroidism and recurrent laryngeal nerve injury. A large study from the Mayo Clinic investigated 1087 patients undergoing thyroid surgery [8]. In comparison to patients undergoing total thyroidectomy alone, the addition of a unilateral central neck dissection increased transient hypoparathyroidism by 1.5-fold and a bilateral

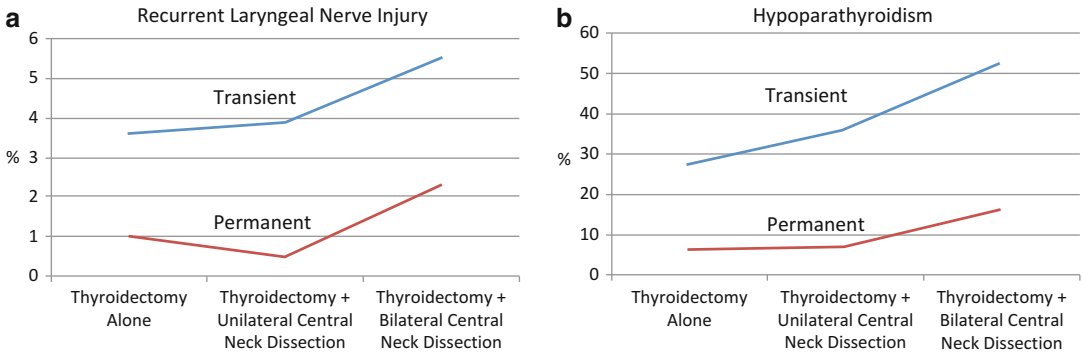

Fig. 13.3 Complications after thyroid surgery. (**a**) Rates of recurrent laryngeal nerve injury and (**b**) hypoparathyroidism after total thyroidectomy alone, total thyroidectomy with unilateral central neck dissection, and total thyroidectomy with bilateral central neck dissection (after Giordano et al. [8])

central neck dissection by 2.8-fold (with rates of 27.7 %, 36.1 %, and 51.9 %, respectively). Permanent hypoparathyroidism was seen in 6.3 % of those undergoing total thyroidectomy alone, a similar 7 % of those undergoing unilateral central neck dissection but did increase to 16.2 % in those undergoing bilateral central neck dissection. Although not statistically significant, an increasing trend was seen in permanent recurrent laryngeal nerve paralysis from 1 % of patients undergoing total thyroidectomy alone to 2.3 % of patients undergoing bilateral central neck dissection. These series reporting complication rates come from large centers with highly specialized surgeons. It is unlikely that comparable results would be obtained from less experienced individuals (Fig. 13.3).

This same question was investigated in a meta-analysis of six studies comprising 1740 patients [9]. No difference could be demonstrated in the recurrence rate of patients who underwent prophylactic central neck dissection versus those who did not. Although not statistically significant, permanent hypocalcemia was 1.8-fold higher and permanent recurrent nerve injury 1.14-fold higher in those undergoing prophylactic central neck dissection. The authors did an interesting calculation, estimating that 31 neck dissections were needed to prevent one recurrence. Interestingly, this number is almost identical to the 27 to 1 ratio published by Crile almost 60 years earlier.

The staging system for thyroid cancer assigns a similar risk regardless of the extent of nodal involvement. The American Thyroid Association has published a detailed review demonstrating that recurrence rates increase as the size of the metastatic focus within the node increases [10]. This also correlates with the number of involved nodes as well as the presence of extranodal extension. All nodal involvement, therefore, cannot be interpreted identically. It remains to be seen how such a nodal substaging will translate into clinical practice. The presence of microscopic nodal disease or Psammoma bodies within lymph nodes has minimal impact on long-term outcome. This further raises the question of whether more aggressive surgical management in this subset of patients is beneficial.

The much quoted American Thyroid Association guidelines published in 2009 address this topic as well [11]. Recommendation 27 states "Prophylactic central-compartment neck dissection (ipsilateral or bilateral) may be performed in patients with papillary thyroid carcinoma with clinically uninvolved central neck lymph nodes, especially for advanced primary tumors (T3 or T4)." The proposed 2014 guidelines do not provide any more specificity. This is a reflection of the lack of clear benefit, in particular for smaller primary tumors.

Summary

In analyzing the literature, it is apparent that there it is unlikely to be any survival advantage to performing prophylactic central neck dissection as the mortality in patients without gross nodal involvement is minimal. Studies have questioned, even in the absence of radioiodine ablation, whether central neck recurrence rates are affected by the prophylactic removal of these nodes. If performed, it is important to be done by experienced surgeons who carefully track their complication and recurrence rates to justify this more aggressive approach. Care should be taken when performing thyroidectomy to sample and send for frozen section any clinically suspicious nodes, as patients with gross nodal involvement are best served by undergoing a therapeutic nodal dissection.

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14 The Role of Risk Stratification in the Treatment of Well-Differentiated Thyroid Cancer

Kepal N. Patel

Introduction

Over the past several decades, the awareness of prognostic factors for well-differentiated thyroid cancer has improved our understanding and management of this unique human cancer. There has been an increased emphasis on utilizing this relatively small set of clinicalpathologic factors in a wide variety of staging systems (e.g., TNM AJCC, MACIS, AMES, AGES—Table 14.1) to predict the risk of death in well-differentiated thyroid cancer [1–8]. The most important of these factors include age of the patient at diagnosis, histology, size of the tumor, completeness of resection, gross extrathyroidal extension, and the presence of metastatic disease at presentation. They are often used to tailor recommendations for both initial therapy and follow-up care for thyroid cancer patients.

These staging systems have traditionally been employed to risk stratify with respect to disease-specific mortality. They are much less effective at predicting the risk of recurrence which is usually much higher than the risk of death in most thyroid cancer patients [9]. Thus, it is desirable to predict the risk of recurrence in addition to the risk of death. What we are really trying to predict is the failure of our initial therapy which then leads to recurrence and possible disease-specific death [10].

Limitations of Current Staging Systems

The current staging systems (Table 14.1) are designed to predict risk of disease-specific death and may not accurately reflect the risk of either persistent disease after initial therapy or clinically evident disease recurrence. These staging systems fail to adequately incorporate the impact of initial therapy (other than completeness of resection). They do not include other variables which reflect the effectiveness (or ineffectiveness) of the initial therapy which may have a significant impact on recurrence and mortality rates [11].

Another significant limitation of the current staging systems is that many of them do not incorporate specific histological subtypes of well-differentiated thyroid cancer (e.g., tall cell variant, columnar cell variant, follicular variant). Tall cell variant tumors are more likely to display aggressive behavior whereas encapsulated follicular variants are likely to behave in an indolent fashion [12–14] Fig. 14.1. Over the last several years, our understanding of the molecular biology of thyroid cancer has increased dramatically

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Table 14.1 Risk stratification staging systems

MSKCC	Mayo Clinic, 1987	Mayo Clinic, 1993	Lahey Clinic	Karolinska Institute
GAMES	AGES	MACIS	AMES	DAMES
Grade	Age	Distant metastasis	Age	DNA
Age	Grade	Age	Metastases	Age
Metastases	Extension	Completeness of resection	Extension	Metastases
Extension	Size	Invasion	Size	Extension
Size		Size		Size

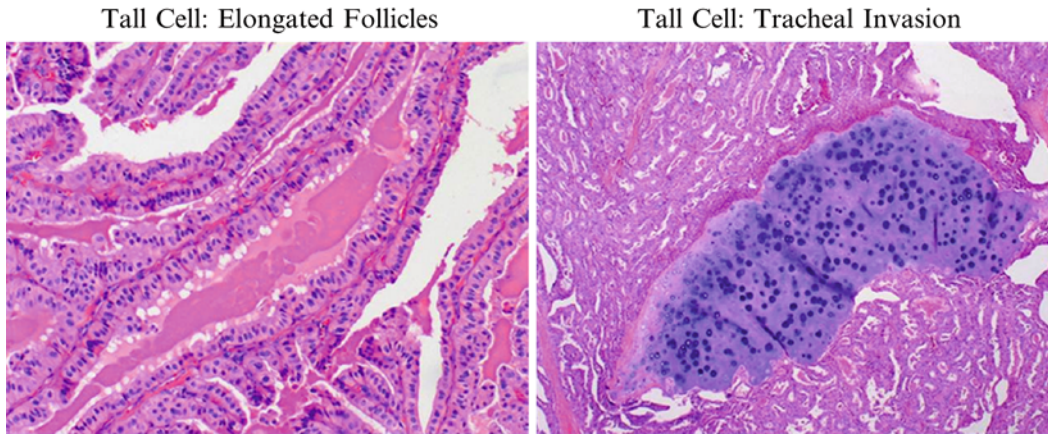

Fig. 14.1 Tall cell variant with aggressive behavior

[15, 16]. Several authors have suggested that the presence of specific molecular abnormalities can provide important information as to the risk of recurrence [17, 18]. For example, it has recently been demonstrated that tumors harboring *BRAF* and *TERT* mutations appear to display a more aggressive clinical course [19, 20]. With widespread availability and use of molecular profiling, it is likely that these genetic aberrations will be added to our risk stratification schemes in the near future.

One of the major problems inherent in the current staging systems is that they present a static representation of the patient at the time of presentation that does not evolve over time [21, 22]. The patient is assigned a stage/risk within the first few weeks after diagnosis, and there are no provisions for modifying this initial risk as new data are accumulated during treatment and follow-up. Clearly in clinical care, our risk estimates change over time depending on the response to therapy for individual patients. For example, a "low-risk" patient who develops a rapidly rising thyroglobulin over time or new distant disease would forever be classified as "low risk" based on initial staging, when in reality the patient is now at increasing risk of developing progressive disease and his or her risk of death from thyroid cancer is increased by virtue of these new clinical findings.

The net effect is that in our current staging systems, the initial risk estimate remains unchanged for the entire life of the patient regardless of how well they respond to initial therapy or how long they have been free of disease. This approach does not reflect clinical practice or the biology of thyroid cancer [9]. Failure to incorporate treatment variables and thus not allow the risk stratification systems to appropriately change over time will result in a higher than necessary risk estimate for high-risk patients that have an excellent response to initial therapy and a lower than appropriate risk estimate for low-risk patients failing to respond to initial therapy [10].

Initial Risk Stratification

Comprehensive initial risk stratification requires a review of all available data that are usually obtained as part of initial diagnosis and therapy (Table 14.2). The American Thyroid Association (ATA) guidelines on the management of thyroid cancer and thyroid nodules recommend using both (1) the AJCC TNM system to estimate the risk of death from thyroid cancer and (2) a separate postoperative clinical-pathologic staging system to improve predictive ability and to plan follow-up for patients with differentiated thyroid cancer [23]. Because none of the commonly used initial staging systems adequately predicts the risk of recurrence, the ATA guidelines recommended a three-tiered staging system (low risk, intermediate risk, and high risk patients) to estimate risk of recurrence (Table 14.3) [23]. This three-tiered staging system also allows itself to evolve as new data are available. The current ATA guidelines are in revision with the new guidelines likely to be published in 2015. Preliminary review of the new guidelines indicate that factors such as favorable histology (encapsulated follicular variant, minimally invasive follicular cancer) and micrometastases will be used to risk stratify. Currently, any regional metastasis places the patient in an intermediate risk category. In the proposed new guidelines, these favorable features would designate a low risk of recurrence. This change highlights the dynamic nature of risk stratification.

Table 14.2 Comprehensive initial risk stratification variables

Preoperative findings
Physical examination
Age at diagnosis
Vocal cord function
Imaging (if available)
Presence of distant metastases
Intraoperative findings
Gross extrathyroidal extension
Locally invasive
Completeness of tumor resection
Lymph node metastases
Pathology findings
Specific histology
Vascular invasion
Size of primary tumor
Molecular characterization
Laboratory findings
Postoperative serum thyroglobulin
Nuclear medicine findings
RAI scans
FDG PET scans

Tuttle et al. recently evaluated the ability of both the AJCC TNM system and the proposed ATA risk of recurrence stratification system to predict the risk of recurrence in a cohort of 588 patients with differentiated thyroid cancer followed for a median of 7 years after total thyroidectomy and RAI ablation [10]. The AJCC TNM system did risk stratify with respect to death; however, it did not adequately risk stratify with respect to risk of recurrence or risk of biochemical or structural persistent disease. Of the 28 patients who died, 26 were AJCC stage IV (1 stage II and 1 stage III patient also died of disease). However, the risk of having persistent or recurrent disease was very similar across AJCC stages I, II, and III. So although AJCC staging is useful for predicting risk of death, it does not provide adequate predictions regarding the risk of recurrence or persistent disease, which is required to plan follow-up studies [10].

The ATA three-tiered system for predicting risk of recurrence performed much better. In their cohort, 23 % of the patients were classified as low risk, 50 % intermediate risk, and 27 % high risk for recurrence based on the ATA system [10, 23]. They found that patients classified as low risk had a 14 % risk of having persistent or recurrent disease, intermediate-risk patients had a much higher likelihood (44 %) of having persistent or recurrent disease, and the high-risk patients had an 86 % likelihood of having persistent or recurrent disease. Interestingly, the persistent/recurrent disease in the low-risk patients was a biochemical diagnosis (thyroglobulin) without structural correlate in 85 %. The persistent/recurrent disease was associated with a structural correlate in 45 % of the intermediate-risk group and 78 % of the high-risk group. They concluded that the ATA risk stratification system

Table 14.3 American Thyroid Association risk of recurrence classification

Low risk	Intermediate risk	High risk
All the following are present • No local or distant metastases • All macroscopic tumor has been resected • There is no tumor invasion of locoregional tissues or structures • The tumor does not have aggressive histology (e.g., tall cell, insular, columnar cell carcinoma) or vascular invasion If ^{131}I is given, there is no ^{131}I uptake outside the thyroid bed on the first posttreatment whole-body RAI scan (RxWBS)	Any of the following is present • Microscopic invasion of tumor into the perithyroidal soft tissues at initial surgery • Cervical lymph node metastases or ^{131}I uptake outside the thyroid bed on the RxWBS done after thyroid remnant ablation • Tumor with aggressive histology or vascular invasion	Any of the following is present • Macroscopic tumor invasion • Incomplete tumor resection • Distant metastases • Possibly thyroglobulinemia out of proportion to what is seen on the posttreatment scan

Table 14.4 Risk stratification for recurrence following complete resection of the primary tumor in patients with no evidence of distant metastases at initial evaluation

	Low risk	Intermediate risk	High risk
Age at diagnosis	Any age	20–60 years	<20 or >60 years
Primary tumor size (cm)	<1	1–4	>4
Histology	Classic PTC confined to the gland	Classic PT, minor extrathyroidal extension, or vascular invasion	Tumor with aggressive histology, gross extrathyroidal extension, or vascular invasion
Lymph node involvement	None	Present or absent	Present
Risk of failing initial therapy	Low	Intermediate	High

identifies both the risk of having persistent/recurrent disease and the likelihood that the persistent/recurrent disease will be either a biochemical or structurally evident recurrence [10].

Since the completeness of surgical resection is a major response to therapy variable, all members of the disease management team need to have a solid understanding of the intra-operative findings. The pathology report by itself may not adequately reflect the extent of disease. For example, positive margins may refer to minor invasion into the strap muscles which was fully resected or unresectable gross disease. The risk stratification and subsequent recommendations in these two situations differ dramatically even though they both had positive margins.

The goal of risk stratification is to help provide the minimal effective therapy and the least intensive follow-up that is likely to result in great clinical outcomes. Integration of all of these factors allows for an initial estimation of the risk of recurrence following complete resection of the primary tumor in patients with no evidence of distant metastases at initial evaluation (Table 14.4).

Initial Treatment

Risk stratification begins before the patient has surgery or any therapy. It's an ongoing dynamic process that begins with the diagnosis of thyroid cancer and continues through all phases of treatment and follow-up. The decision regarding extent of surgery, use of radioactive iodine (RAI) for remnant ablation, and/or the use of external beam radiation therapy (EBRT) is a joint decision between the patient and the disease management team. This decision is based on risk of recurrence and risk of death and represents a balance

Table 14.5 Initial therapeutic recommendations

Risk of recurrence	Initial surgery	RAI remnant ablation
Low	Lobectomy or total thyroidectomy	Not required
Intermediate	Total thyroidectomy	For selected patients[a]
High	Total thyroidectomy	Yes

[a]Selected patients would probably include patients with tumor size >2–3 cm, lymph node metastases, extrathyroidal extension, or vascular invasion

between necessary effective therapy and the likely side effects of that therapy.

Most guidelines recommend total thyroidectomy as the initial procedure of choice in patients with well-differentiated thyroid cancers >1 cm [23]. In several large studies, a total thyroidectomy was associated with significantly lower recurrence rates than thyroid lobectomy [24–26]. However, a thyroid lobectomy achieves the same great disease-specific survival in patients who are at low risk of dying from thyroid cancer [27]. With careful follow-up, usually with neck ultrasound and laboratory studies, the small number of patients that may recur are easily treatable with additional surgery and possible RAI. Therefore, less than total thyroidectomy is an acceptable surgical option for low risk patients (Table 14.5).

Occasionally, the final pathology may result in upstaging a patient who was initially deemed low risk based on preoperative and intra-operative findings. If the final pathology reveals a more aggressive histology, e.g., tall cell variant, with extrathyroidal extension and lymphovascular invasion, the patient may require a complete thyroidectomy to help facilitate surveillance and possible RAI therapy.

Response to Initial Therapy

Initial risk assessments provide the basis for ongoing risk stratification. Based on response to initial therapy, new data obtained during follow-up are used to modify risk stratification and provide recommendations regarding future follow-up [9]. Some of data that are used to modify initial risk estimates are summarized in Table 14.6 [28–37]. Regardless of initial AJCC TNM stage or ATA risk group classification, rising values of serum thyroglobulin (Tg) or Tg antibodies would be expected to increase the risk of developing progressive or newly identifiable structural disease. Conversely, declining Tg values, undetectable stimulated Tg values, negative neck ultrasonography, and other cross-sectional imaging would all tend to decrease the risk of disease recurrence and death. The goal is to identify those patients that are probably cured of thyroid cancer, so that excessive additional treatments and follow-up studies can be avoided and, at the same time, identify those patients with persistent disease that may require additional therapy. Usually within a few years after initial therapy, it is possible to differentiate between patients who have had an excellent response to therapy and those that still have persistent disease.

Tuttle et al. have proposed a response to therapy assessment scheme that classifies patients as having an excellent, acceptable, or incomplete response to initial therapy (Table 14.7) [10]. In this system, the response to therapy for each patient is determined on the basis of the standard follow-up testing that is usually done in differentiated thyroid cancer. Patients with an "excellent response" to therapy have no evidence of disease with negative imaging and undetectable stimulated thyroglobulin values. RAI scanning, if done, shows only normal uptake in the thyroid bed without evidence of metastatic disease. Patients with an "acceptable response" to therapy have low-level persistent thyroglobulinemia (suppressed Tg < 1 ng/mL, stimulated Tg < 10 ng/L), or nonspecific changes on imaging, that though not abnormal, were not completely normal. This is considered an acceptable response because these patients may be followed with cautious observation and not immediately retreated. Patients with an "incomplete response" are those who clearly failed their initial therapy. These patients have persistently elevated or rising serum Tg during the first 2 years of follow-up or have new structural disease identified within that same time period [10].

Based on the concept of ongoing risk stratification, patients who have an excellent response to initial therapy, should be at a lower risk of recurrence/persistent disease than what may have been originally predicted by initial risk stratification.

Tuttle et al. demonstrate this in their study by showing that regardless of initial risk stratification, patients demonstrating an excellent response to therapy have only a 4 % likelihood of having persistent/recurrent disease, whereas patients who have an acceptable response to therapy have a 13 % risk of having persistent/recurrent disease (mostly biochemical without structural correlate). As expected, the incomplete response to therapy patients had a 96 % chance of having persistent/recurrent disease with over 55 % chance of having structurally identifiable disease [10].

Table 14.6 Response to therapy variables

Physical examination
Change in serum thyroglobulin over time
Change in serum Tg antibodies over time
Results of stimulated Tg
Results of follow-up neck ultrasound
Results of RAI scans
Other cross-sectional imaging
Results of FDG PET imaging

Table 14.7 Categories of response to initial therapy

Excellent response	Acceptable response	Incomplete response
All the following	Any of the following	Any of the following
• Suppressed and stimulated Tg < 1 ng/mL	• Suppressed Tg < 1 ng/mL and stimulated Tg ≥ 1 and <10 ng/mL	• Suppressed Tg ≥ 1 ng/mL or stimulated Tg ≥ 10 ng/mL
• Neck ultrasound without evidence of disease	• Neck ultrasound with nonspecific changes or stable subcentimeter lymph nodes	• Rising Tg values
• Cross-sectional and/or nuclear medicine imaging negative (if performed)	• Cross-sectional and/or nuclear medicine imaging with nonspecific changes, although not completely normal	• Persistent or newly identified disease on cross-sectional and/or nuclear medicine imaging

Continued Risk Stratification

The optimal use of current staging systems is to start with an initial risk assessment, based on AJCC TNM staging and the ATA risk of recurrence classification system, and then integrate this initial risk estimate with the individual patient's response to therapy. This will provide an updated, dynamic realistic risk estimate. It is the response to therapy along with the initial risk assessment that should guide our long-term follow-up recommendations rather than just the initial risk estimates made at the time of initial therapy.

Studies have shown that the impact of response to therapy on initial risk stratification is significant [9, 21, 22]. An excellent response to therapy significantly decreases the risk of recurrent/persistent structural disease to 2 % in patients who were initially classified as ATA low to intermediate risk of recurrence and 14 % in patients who were initially classified as ATA high risk of recurrence. This significant improvement in outcomes is reflective of the importance of an excellent response to therapy and ultimately the biology of the cancer being treated.

Conversely, an incomplete response to therapy in the patient initially classified as low to intermediate risk is associated with a significant increase in the risk of recurrent/persistent structural disease during follow-up. Patients who were initially classified as low risk based on the ATA risk of recurrence classification are thought to have only a 3 % risk of having persistent/recurrent disease. If they have an incomplete response to therapy, this risk increases to 13 %. Likewise, intermediate-risk patients having an incomplete response to therapy see the initial risk estimate for recurrent/persistent structural disease of 18 % rise to 41 % [10].

The impact of dynamic risk assessment is best illustrated by the example of patients who were initially stratified as having an intermediate risk of developing recurrent or persistent disease based on the ATA classification system. These

patients would have an approximately 18 % risk of recurrent/persistent structural disease and would demand close, intensive follow-up. However, if these intermediate-risk patients have either an excellent or acceptable response to therapy then the risk of developing recurrent/persistent disease drops dramatically to only 2 %. Therefore, intermediate-risk patients who have an excellent response to therapy should be followed as "low-risk" patients with the intensity of follow-up tailored to the revised 2 % risk estimate and not the initial 18 % risk estimate. The importance of accurate, ongoing risk stratification cannot be overemphasized.

Secondary Risk Stratification, Surveillance, and Clinical Outcomes

As described earlier, identifying patients at low risk of recurrence over time requires integration of initial risk estimates with response to therapy variables to achieve a dynamic, ongoing risk assessment. While continuous, ongoing risk stratification occurs at each follow-up visit, it seems reasonable to define a point in time where secondary risk stratification can be utilized to develop a less intensive long-term follow-up consisting of yearly physical examination and suppressed Tg values for low-risk patients. From a clinical perspective, a secondary risk stratification seems reasonable approximately 2 years after initial therapy. By 2 years after initial therapy, several responses to therapy variables such as neck ultrasounds, several suppressed Tg values, stimulated Tg values, and diagnostic whole-body follow-up scans are available for incorporation into the ongoing risk stratification. Additionally, serum Tg values often continue to decline for at least 12–18 months after RAI ablation, so a 2-year time point would allow a reasonable period of time to assess whether the Tg is rising or falling in a given patient [21].

Low-risk patients with excellent response to therapy on secondary risk stratification may be safely followed with yearly physical examination and suppressed Tg (Table 14.8). It must be emphasized that the secondary risk stratification at 2 years after initial therapy is designed simply to guide the follow-up paradigm and not to accurately predict which patients are "cured" of disease. From a practical standpoint, additional secondary risk stratification time points could be considered at year 5 for intermediate-risk patients and at year 10 for high-risk patients before being comfortable so that a minimal follow-up paradigm of suppressed Tg and physical examination is adequate for these patients who were initially stratified more than low risk for recurrence.

For low- and intermediate-risk patients, the combination of negative neck ultrasound and an undetectable stimulated Tg, on secondary assessment, is the most predictive for no evidence of disease [35]. However, this is not true for high-risk patients. Negative imaging and an undetectable stimulated Tg predict no evidence of disease in only 82 % of high-risk patients. Therefore, additional follow-up and imaging studies are often used in these high-risk patients, even after achieving an excellent response to therapy within the first 1–2 years of follow-up. Over time, less intense follow-up can be recommended for the few high-risk patients who continue to demonstrate an excellent response to therapy. Obviously, the intensity and type of follow-up should be tailored to the individual risk of recurrence and disease-specific mortality.

Clearly, specific follow-up recommendations will vary for individual patients, based on initial risk stratification, disease-free survival time, and response to therapy variables, but this method does provide an approach to secondary risk stratification several years after initial therapy and should guide the long-term follow-up approach.

Conclusions

Risk stratification is an active ongoing process that informs our decisions, beginning with the correct initial risk estimates which help determine our initial treatment recommendations regarding the extent of initial surgery (extent of thyroidectomy and lymph node dissection), the need for RAI remnant ablation, and the degree of Thyroid stimulating hormone (TSH) suppression. Data

Table 14.8 Secondary risk stratification—response to therapy assessment

	Excellent response	Acceptable response	Incomplete response
Ongoing follow-up	Yearly physical examination, yearly suppressed Tg[a]	Yearly physical examination, yearly suppressed Tg, stimulated Tg to document undetectable Tg on suppression, continued observation/assessment of indeterminate structural abnormalities for at least another 2–3 years[b]	Consider additional cross-sectional imaging, possibly FDG-PET scan and the need for additional therapy

[a]Intermediate or high-risk patients, even in the setting of an excellent treatment response at year 2, may still periodically require neck ultrasonography, depending on the specifics of each individual case. Additionally, patients in whom the initial therapy was less than total thyroidectomy and RAI ablation may benefit from occasional neck ultrasounds over the next 5–10 years, because Tg on suppression is less sensitive for detection of recurrent disease in this setting

[b]Patients with stable low level Tg values and stable small structurally abnormal lymph nodes that have been stable for 5 years (and therefore still in the acceptable response category) can transition to yearly follow-up, suppressed Tg values, and occasional neck ultrasonography to document continued structural stability

gathered from therapy variables (serum Tg, neck ultrasonography, functional/cross-sectional imaging) during the first 1–2 years of follow-up should be used to review the individual patient's response to initial therapies and appropriately modify the initial risk estimates using a dynamic, ongoing risk assessment approach. Long-term follow-up recommendations are then based on the updated, modified risk estimates to better tailor the intensity and type of follow-up to realistic risk estimates. It is only through proper risk stratification that we can maximize the benefit of aggressive therapy in patients that are likely to benefit from it while minimizing potential complications and side effects in low-risk patients destined to live a full, healthy, productive life.

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Imaging for Preoperative Assessment and Staging of Thyroid Cancer

15

James X. Wu and Michael W. Yeh

Introduction

Thorough preoperative imaging is essential in determining the appropriate extent of surgery for thyroid cancer. Incomplete initial surgical therapy for thyroid cancer often arises from inadequate preoperative imaging, and results in the added cost and morbidity of reoperations for persistent disease [1]. This chapter will review the latest indications, innovations, and controversies in ultrasound and cross-sectional preoperative imaging for thyroid cancer.

Neck Ultrasound

Ultrasound is the primary tool for preoperative imaging of thyroid cancer, as stated in the American Thyroid Association guidelines for management of thyroid nodules and thyroid cancer [2]. In most cases of thyroid cancer, ultrasound is sufficient as the sole imaging modality. Preoperative neck ultrasound can evaluate the primary tumor and the central and lateral neck lymph node basins to help the surgeon determine: (1) whether additional imaging is necessary, (2) the need for compartmental clearance of involved lymph node basins, and (3) whether possible sternotomy or reconstructive surgery should be anticipated in cases of advanced disease. Because the surgeon is ultimately accountable for the quality of thyroid cancer surgery, the burden of ensuring excellent pre-operative imaging also lies with the surgeon. This can be achieved through expert surgeon-performed ultrasound (our preferred approach) or close communication between the surgeon and an expert radiologist.

Evaluation of Primary Tumors

Evaluation of the primary tumor should encompass the following features: tumor size, tumor location within the thyroid and in relation to viscera and vessels, local invasion if present, and multifocality if present. Posterior lesions located near the recurrent laryngeal nerve should raise clinical suspicion of involvement and prompt further evaluation of vocal cord function. Tumor juxtaposed to major vascular or aerodigestive structures should be scrutinized for local invasion, which often appears as a blurry or indistinct

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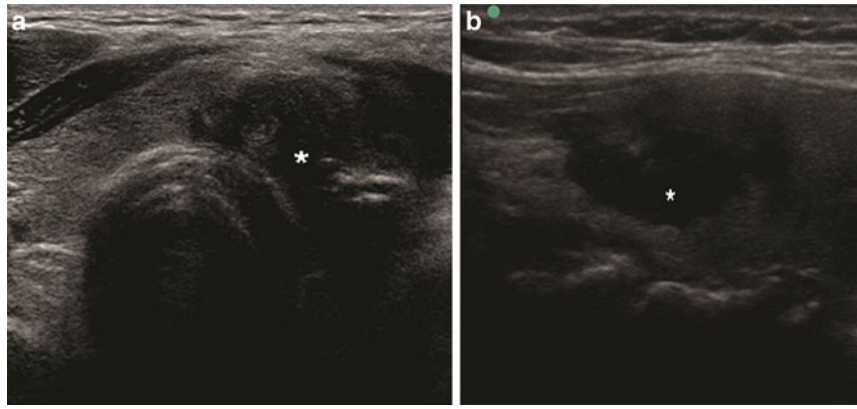

Fig. 15.1 Ultrasound features of locally invasive papillary thyroid cancer. (**a**) Primary papillary thyroid cancer (*) apposed to trachea with midline shift. (**b**) Primary papillary thyroid cancer (*) with wavy, indistinct border with thyroid

deep margin, or obliteration of normal fat planes. The finding of invasion may prompt additional imaging or may herald the need for en bloc resection of adjacent structures with reconstruction. In contrast, minor invasion of the strap muscles is relatively common and does not have significant clinical implications. Finally, the entire thyroid should be examined for additional tumor foci; if lesions are found in the contralateral lobe, the contralateral lymph node basins should be inspected with enhanced scrutiny for lymph node involvement [3, 4] (Fig. 15.1).

Evaluation of Lymph Nodes

The aim of ultrasound examination of lymph node basins is first to detect the presence and location of suspicious lymph nodes and second to evaluate sonographic characteristics of suspicious nodes that help distinguish between benign reactive nodes versus malignant lymph nodes. All relevant lymph node basins should be examined systemically to determine the need for additional compartmental lymphadenectomy. In papillary thyroid cancer, metastases generally appear in a sequential fashion, occurring most often in ipsilateral neck level 6, followed by ipsilateral levels 3 and 4. Involvement of levels 2 and 5 is seen in approximately 5 % of patients with papillary thyroid cancer [5]. "Skip lesions" can be found in superior pole tumors, which may present with isolated level 2 or 3 adenopathy. Neck level 6 comprises the central compartment, which includes three main areas: right paratracheal, left paratracheal, and pretracheal/prelaryngeal. Imaging of the central compartment can be difficult prior to thyroidectomy; the sensitivity of ultrasound for abnormal lymph nodes is only 25–60 % in the central compartment versus 70–95 % in the lateral compartments [6, 7]. The lateral compartment includes levels 2–4, which are oriented cranial to caudal, deep to the sternocleidomastoid muscle. The lateral neck also includes neck level 5, located to the sternocleidomastoid muscle, which contains the posterior triangle nodes.

Once candidate nodes are identified, they should be inspected for sonographic signs that suggest malignant involvement. Lymph node size is commonly assessed first. However, because lymph node enlargement can be seen in benign reactive processes, large size alone does not necessarily imply malignancy; lymph node size greater than 1 cm is only 75 % specific and 68 % sensitive for malignancy [8].

Compared to size, lymph node shape predicts malignancy with greater specificity. Benign lymph nodes have a more oval or fusiform shape and can contain a hyperechoic central stripe (fatty hilum) with central vascular flow [9]. Conversely, malignant nodes tend to have a more rounded shape. An objective measure of shape is the length of the shortest diameter. Round lymph nodes tend to have a shortest diameter greater

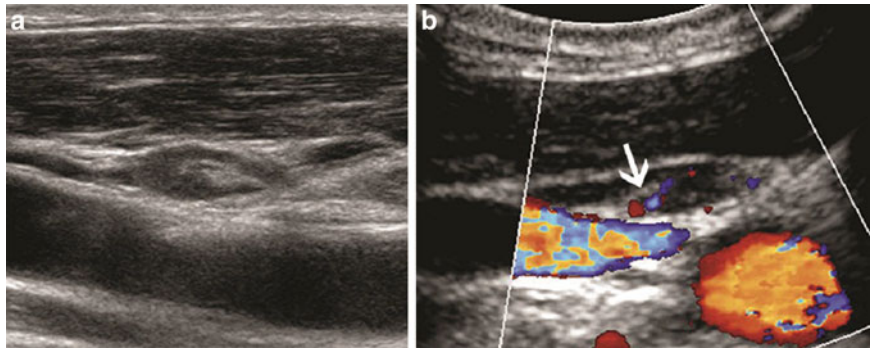

Fig. 15.2 Ultrasound features of normal cervical lymph nodes. (**a**) Normal fusiform lymph node with hyperechoic hilum. (**b**) Central, hilar blood flow in a normal lymph node (*white arrow*), visualized with a curvilinear ultrasound probe

than 5 mm; this finding is 96 % specific, but only 61 % sensitive, for malignancy [10]. Another criterion for assessing lymph node shape is the Solbiati index, which is the ratio of the long and short diameter of the lymph node. A Solbiati index of <2.0 is seen in of 63 % malignant nodes, whereas the Solbiati index is >2.0 in 83 % of benign nodes [11] (Fig. 15.2).

Additional sonograghic characteristics that predict malignancy include calcifications, hyperechoic or cystic changes, and peripheral hypervascularity. Microcalcifications, which can be observed in lymph nodes affected by papillary thyroid cancer and sometimes medullary thyroid cancer, are only 48 % sensitive but 100 % specific for metastatic involvement [10]. A lymph node containing microcalcifications should be considered malignant until proven otherwise. Secondly, while benign lymph nodes are homogenous and hypoechoic on ultrasound, malignant nodes may demonstrate mixed echogenicity, hyperechogenicity, or even complete cystic replacement. Cystic degeneration is more commonly seen in children and young adults and may indicate more aggressive tumor biology [12]. Finally, vascular flow in benign lymph nodes normally traverses the hilum, located at the center of the node. Invasion of tumor into the node redirects blood flow to the periphery of the node. Compared to other sonographic predictors, peripheral hypervascularity is considered to have the greatest sensitivity and specificity for malignant involvement, with 86 % sensitivity and 82 % specificity [10]. It should be noted that loss of the normal nodal fatty hilum, though 100 % sensitive for malignancy, only carries a sensitivity of 29 % [10] (Fig. 15.3).

Fine-needle aspiration biopsy (FNA) of sonographically suspicious lymph nodes may be useful in justifying the addition of central or lateral compartment neck dissection to initial thyroidectomy for thyroid cancer. This represents an area of practice variation, where some centers routinely confirm lymph node involvement with FNA biopsy prior to proceeding with neck dissection [13]. In our practice, we find that a significant fraction of lymph nodes found in the context of a known primary thyroid cancer have unequivocally abnormal findings that obviate the need for FNA.

At our institution, ultrasound-guided FNA is performed using a bimanual technique in which the ultrasound probe is held in the nondominant hand and the biopsy needle held in the dominant hand. After appropriate positioning with the neck extended and the application of proper antiseptic technique, the skin is anesthetized with lidocaine. The target lesion is centered and a 25-gauge needle is introduced at an oblique angle parallel to the plane of imaging. The needle tip is guided into the highest-yield site within the target (e.g., a solid area with microcalcifications) and tissue collected with the French (non-aspiration) technique. The specimen is then placed in a receptacle and the needle rinsed with a small volume of normal saline. The FNA needle washout can be tested for thyroglobulin or calcitonin levels.

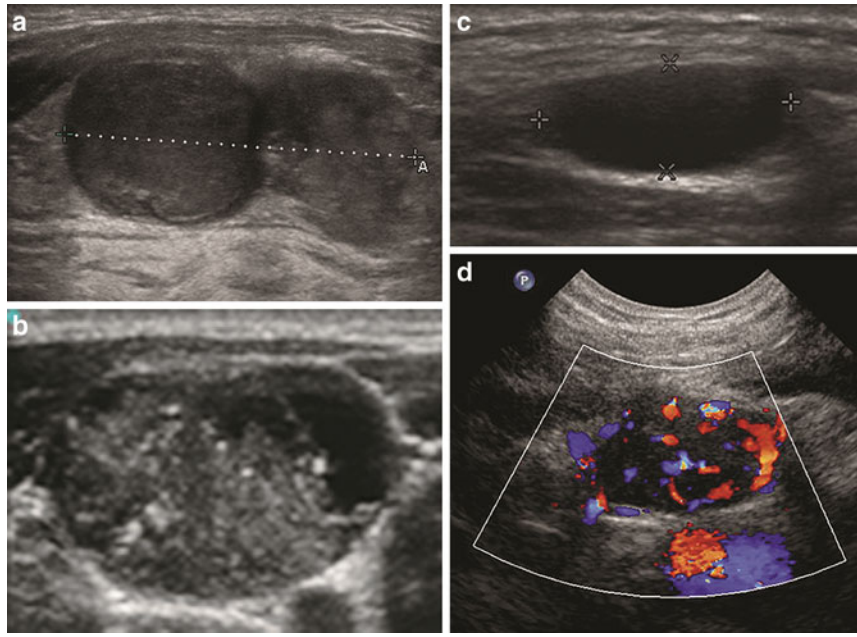

Fig. 15.3 Ultrasound features of malignant lymph nodes. (**a**) Rounded, matted lymph nodes with metastatic papillary thyroid cancer. (**b**) Punctate calcifications, rounded shape, and partial cystic replacement seen in a lymph node with metastatic papillary thyroid cancer (**c**) Complete cystic degeneration in lymph node with metastatic papillary thyroid cancer. (**d**) Malignant lymph node with redirection of blood flow to periphery, curvilinear probe

Ultrasound in the Setting of Previous Neck Surgery

Postsurgical changes can confound findings on neck ultrasound. Postoperative reactive adenopathy, inflammation, and scarring all increase the probability of false-positive ultrasound findings. Therefore, it is our practice to avoid performing ultrasound until 9 months after surgery. In the postoperative setting, neck ultrasound should be conducted systematically in the same fashion as the initial preoperative scan. It should be noted that after total thyroidectomy, lymph nodes within the central compartment are more readily imaged.

In light of the increased risks associated with revision surgery, suspicious ultrasound findings after previous thyroid cancer resection should generally be evaluated with FNA, unless the lymph nodes are inaccessible or unequivocally abnormal. Additionally, abnormal ultrasound findings should always be interpreted in the context of previous surgical findings, the original pathology report, and biochemical markers. For example, ipsilateral lateral neck lymph node recurrences can occur in up to 35 % of patients with a history of lateral neck disease; thus, abnormal lymph nodes in this context should be regarded with a high level of suspicion. An elevated or upward trending serum thyroglobulin level is highly indicative of recurrent disease and increases the pretest probability that a sonographically suspicious lymph node will prove to be malignant. In the historical context of a unilateral primary tumor, suspicious ipsilateral nodes typically have a high likelihood of malignant involvement and should be "ruled out" with FNA. Conversely, suspicious nodes in the contralateral lymph node basins should be "ruled in" with FNA.

Ultrasound Sonoelastography

Elastography is an ultrasound technique that measures tissue elasticity or firmness by assessing the degree of tissue deformation that occurs when the target tissue is subjected to an external

force, i.e., static compression applied via the ultrasound probe. Tissue firmness is transformed by the elastography device into a colorimetric reading. Because thyroid cancers are commonly firmer than benign lesions, elastography has the potential to distinguish between the two in a non-invasive manner.

Recent studies have demonstrated that elastography carries a sensitivity of 86–97 % and specificity of 34–83 % in the assessment of thyroid nodules for malignancy [14–16]. However, due to lack of standard technique and user variability, elastography currently has limited clinical value above that of conventional ultrasound alone. Newer technologies, such as "shear wave" elastography, remove the need for manual pressure, instead using the propagation of ultrasonic beams to determine tissue elasticity. These advances may improve the utility of elastography over time [17].

Laryngeal Ultrasonography

Another emerging technology is the use of transcutaneous neck ultrasound to assess vocal cord function in the preoperative evaluation of patients with thyroid cancer. In a study of 672 patients with thyroid cancer, laryngeal ultrasound was successful in 87 % of patients [7]. Exam feasibility is negatively influenced by the prominence of the thyroid cartilage; vocal cord movement was observed in 98 % of women but only 51 % of men. Because published reports on laryngeal ultrasound have largely been confined to Asian populations with low body mass index, it remains to be seen whether this technique can be applied successfully to patients with less favorable body habitus [18]. Given its convenience and negligible cost, laryngeal ultrasound can easily be added to the standard preoperative neck ultrasound exam. Our current practice is to apply laryngeal ultrasound selectively for patients with locally invasive tumors, posteriorly located tumors, or those with symptoms and signs of vocal cord dysfunction. At present, laryngeal ultrasound remains an emerging technique and should not supplant laryngoscopy when indicated.

To perform laryngeal ultrasound, the probe is placed transversely on the middle of thyroid cartilage, aimed slightly cephalad. Imaging is aided by lowering the frequency and increasing gain. Orientation to the vocal cords is facilitated by asking the patient to perform a gentle Valsalva maneuver, clearing the throat, or puffing air out through pursed lips. When the correct plane of imaging is achieved, the true cords, false cords, and arytenoid cartilages can be seen. The vocal cords are then assessed for symmetry and movement during normal breathing and phonation.

Cross-Sectional Imaging with CT and MRI

Current ATA guidelines do not recommend routine cross-sectional imaging prior to initial surgery for thyroid cancer [19]. Nonetheless, certain conditions indicate the addition of cross-sectional imaging to neck ultrasound. These indications include: (1) clinical evidence of local invasion (e.g., hoarseness, stridor, dysphagia, or fixed mass on exam); (2) large primary tumor or mediastinal extension, incompletely imaged by ultrasound; (3) nodal disease extending into the mediastinum, deep structures of the neck, or otherwise beyond the anatomic range acoustically accessible by ultrasound; (4) sonographic evidence of significant local invasion; and (5) unavailability of ultrasound expertise. Most of these indications are surrogate markers of locoregionally advanced disease, which is present in 10–15 % patients with well-differentiated thyroid cancer [20, 21]. Lack of available expertise is institution-dependent and likely a diminishing problem given the recent expansion of formal ultrasound training across several clinical disciplines [22, 23]. Preoperative screening for distant metastases using cross-sectional imaging is not recommended, as it does not alter initial management with thyroidectomy. Moreover, metastases are typically detected using functional radioactive iodine scanning, which is best performed after surgical removal of all thyroid tissue [2].

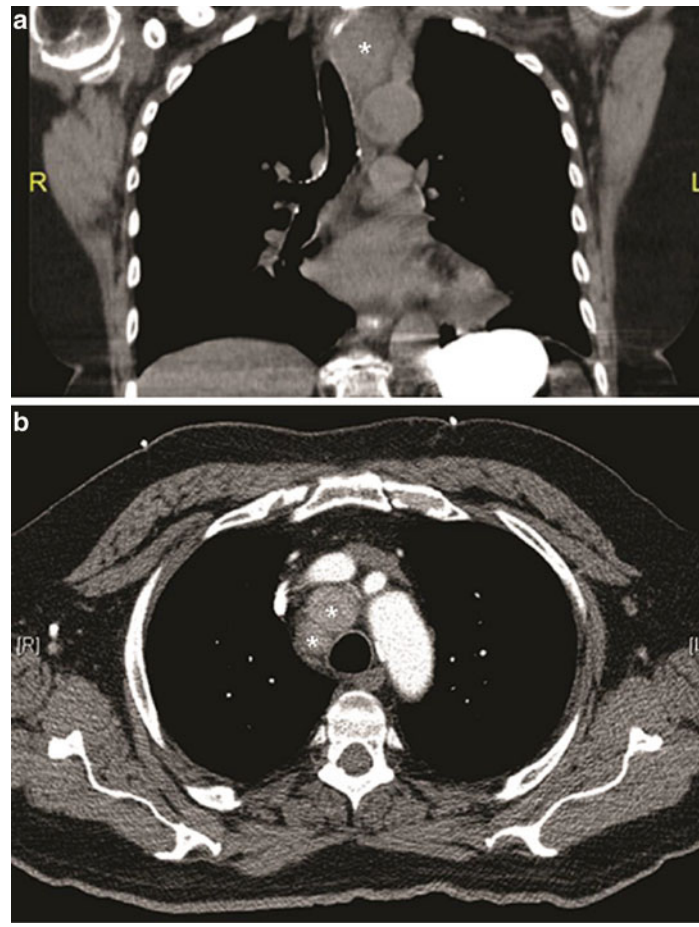

Fig. 15.4 CT images of advanced thyroid cancer. (**a**) Papillary thyroid cancer (*) with extension into mediastinum. (**b**) Medullary thyroid cancer with spread of disease to periaortic lymph nodes (*)

From a practical standpoint, we find that less than 5 % of patients presenting to our academic referral center require any imaging above ultrasound prior to either initial or subsequent surgery for thyroid cancer.

Computed Tomography

CT scanning is widely used as a second-line imaging modality for thyroid cancer after ultrasound. It carries the methodologic advantages of being standardized, reproducible, and user-independent. Rapid helical scanning provides clear images that are free of motion artifact. The added value of cross-sectional imaging lies in characterization of the full extent of locoregional spread and assessment of tumor invasion to aid surgical planning. Assessment of the primary tumor should include scanning from the skull base to the mediastinum. Intravenous contrast is needed to facilitate visual differentiation of tissues and should be used in all cases unless specifically contraindicated by allergy or renal insufficiency. In a study of 86 patients with thyroid cancer displaying extracapsular extension, CT was 29–78 % sensitive and 91–99 % specific for invasion of the trachea, esophagus, common carotid artery, internal jugular vein, or recurrent laryngeal nerve [24] (Fig. 15.4).

Effect of Iodinated Contrast on Radioactive Iodine Therapy

Iodinated contrast should be used judiciously in the setting of thyroid cancer treatment, as it can compromise the uptake of radioactive iodine, and

thus delay postoperative ablation. The current standard is to delay radioactive iodine ablation by at least 1 month after the administration of iodinated contrast, which is sufficient time for urinary iodine levels to return to normal [25]. Close communication between surgeon and endocrinologist is therefore essential when considering the need for contrast CT scans in thyroid cancer patients.

Magnetic Resonance Imaging

MRI is a third-line imaging modality in evaluating patients with thyroid cancer. It is principally used for patients requiring cross-sectional imaging who have a known allergy to iodinated CT contrast. An additional advantage of MRI is the fact that gadolinium contrast does not interact with radioactive iodine. Contrast and noncontrast images should be obtained, since thyroglobulin produced in lymph node metastases are hyperintense on T1 weighted scans. MRI is limited by motion artifact arising from long image acquisition times. Finally, patients with advanced renal failure are at risk of a rare complication of gadolinium administration—nephrogenic systemic fibrosis [26].

Functional Imaging

Radioactive iodine scanning holds a historical place as the primary choice of imaging for persistent or recurrent thyroid cancer [2]. However, the low resolution of these scans limits their utility as a preoperative imaging modality. While positron emission tomography (PET) scans have a similarly low resolution, combined PET/CT scans do offer sufficient anatomical detail for surgical planning. That said, given the relatively low metabolic activity of most thyroid malignancies, most primary tumors and up to 70 % of metastases are non-fluorodeoxyglucose (FDG) avid [27–30].

At present, PET/CT scans are most useful in the detection of recurrent thyroid cancer, specifically in patients with an elevated or rising thyroglobulin level who have negative radioactive iodine scans [31–34]. Reduced iodine uptake by thyroid tumors is associated with increased 18 F-FDG uptake in what has been described as a "flip-flop" phenomenon related to dedifferentiation [35]. The sensitivity and specificity of PET/CT in I^{131}-negative patients has been reported at 81 and 89 % [36]. Combined PET/CT scanning can help detect additional non-hypermetabolic metastatic lesions, explain false positive findings seen on PEt alone, and detect distant metastatic disease. TSH stimulation may further improve the sensitivity of PET/CT [37].

FDG-avid lesions of the thyroid may be discovered incidentally during surveillance imaging for other malignancies. Between 2003 and 2005, thyroid "PET incidentalomas" were found in 2.9 % of 8800 patients who underwent PET/CT scanning at Memorial Sloan Kettering Cancer Center [38]. These lesions typically show one of two FDG uptake patterns: diffuse or focal. While diffuse uptake generally reflects inflammation, focal uptake is associated with thyroid malignancy in about half of cases [39]. As such, the most appropriate next steps are neck ultrasound and FNA. FNA reveals papillary thyroid carcinoma in the great majority of cases, though other thyroid cancer subtypes and metastases to the thyroid gland may occasionally be found. The decision to pursue intervention for primary thyroid cancer discovered as a PET incidentaloma should be made in the context of the patient's overall prognosis, as papillary thyroid cancer is almost always less biologically aggressive than the malignancy for which the PET scan was ordered in the first place.

A Note on Preoperative and Dynamic Staging

The primary goal of preoperative imaging is to guide surgical resection. Failure to delineate the true extent of disease may result in avoidable persistent disease and necessitate reoperation, which is associated with increased disease-specific mortality [40]. While preoperative staging based on the American Joint Commission on Cancer (AJCC) staging system allows prognostication of disease-specific mortality to some

extent, its informative value is small in relation to that of postoperative staging.

Complete AJCC staging is typically performed postoperatively with histopathologic results in hand. The AJCC system is limited by its lack of consideration of the impact of surgery on thyroid cancer prognosis. Mortality and recurrence risk are strongly correlated to the completeness of tumor resection, as reflected in the widely accepted MACIS (Metastases, Age, Completeness of resection, Invasion, and Size) score and the recent American Thyroid Association staging system. Both of these incorporate the outcome of initial resection into prognosis [41, 42]. Tuttle et al. have demonstrated that dynamic re-stratification using response to therapy at discrete clinical end points better predicts risk of recurrence and disease outcomes than preoperative staging [42].

Imaging Costs

The costs of the various imaging modalities discussed above are listed in Table 15.1. Because of its high informative yield and low cost, ultrasound is our preferred test with respect to maximizing patient value. However, no formal cost-effectiveness studies have been performed at this time.

Table 15.1 Costs of various imaging modalities

Imaging modality	Cost[a] (2015)
Ultrasound of head and neck	$117.28
CT neck without contrast	$193.08
CT neck with contrast	$235.98
CT chest with and without contrast	$275.31
MRI orbit/face/neck without contrast	$358.62
MRI orbit/face/neck with and without contrast	$493.06
MRI chest with and without contrast	$581.37
Whole body I-131 scan	$323.22
18 F-FDG PET/CT scan, eyes to thighs	$667.19

[a]All costs obtained from Medicare Physician Fee Schedule [43]

Summary

We have detailed the strengths of various imaging modalities in the evaluation of patients with thyroid cancer. The primacy of ultrasound in this arena is well established, though mild controversy lies in the fact that some groups utilize cross-sectional imaging liberally. In closing, we emphasize that thyroid cancer is a surgical disease in that the quality of surgery heavily influences prognosis. It is our hope that surgeons treating patients with thyroid cancer will participate actively in the cultivation of optimal imaging within their institutions in order to best serve their patients.

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Anaplastic Cancer and Rare Forms of Cancer Affecting the Thyroid

16

Brian R. Untch and John A. Olson Jr.

Management of the Rapidly Expanding Neck Mass

All three entities may present as a rapidly expanding neck mass, but this is most commonly observed in anaplastic thyroid carcinoma (ATC) and thyroid lymphoma. Any patients with a rapidly expanding neck mass should be suspected of having a malignancy until proven otherwise. A differential diagnosis for a neck mass is best organized into categories of either congenital, inflammatory, or neoplastic. Adults are far more likely to present with inflammatory or neoplastic processes. Infectious lymphadenopathy is either self-limited or can respond to antibiotics. A watchful waiting approach is reasonable for small neck masses (2–3 cm) as long as interval imaging is obtained to document resolution (Fig. 16.1). For larger neck masses including those that involve the thyroid, biopsy and imaging should not be delayed. Goiter can also present as a neck mass, but these are typically very slow growing. For those patients that present with a rapidly expanding neck mass, the priority is to establish a diagnosis through biopsy and obtain cross-section imaging. A thorough history and physical examination should be performed and symptoms related to compression of neck structures should be elicited. Office laryngoscopy should also be performed to evaluate vocal cord mobility and function. Large anaplastic thyroid cancers often involve the recurrent laryngeal nerve and can invade the thyroid cartilage/trachea. Diagnosis in this setting can usually be achieved in the office with fine needle or core biopsy and ultrasound if available. Biopsy without ultrasound guidance is also reasonable if the lesion is large and easily palpable, but cross-sectional imaging should be available for reference and choosing a biopsy site. Large neck tumors can easily distort neck anatomy, and imaging can help guide the needle into the tumor, avoiding biopsy of normal thyroid gland or other structures. An alternative to this approach is an open biopsy in the operating room. However, the needle biopsy approach is easily tolerated and avoids the need for sedation and the high costs associated with operating room usage. Additionally, sedation and anesthesia can be difficult for patients with large neck tumors due to the challenges of intubation and potential airway

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compromise. As soon as a diagnosis is established, it is critical that the physician develops a treatment plan and involves other physicians as needed in a timely manner. Patients with rapidly expanding neck masses can develop difficulty with breathing and swallowing very abruptly. Thus, a treatment plan should be formed in a manner of days as opposed to weeks.

Anaplastic Thyroid Cancer

ATC is an exceedingly rare form of thyroid cancer accounting for 2 % of thyroid cancer diagnoses [1]. However, ATC accounts for a much higher percentage of thyroid cancer-related deaths [2]. The median survival from diagnosis ranges from 3 to 10 months depending on the series [3]. Disease-specific mortality is related either to local disease progression or metastatic disease. Patients commonly present in the sixth or seventh decade of life, and females are more commonly affected than males [4].

The pathogenesis of ATC is incompletely understood, but thought to involve extensive genomic changes as compared to well-differentiated thyroid cancer [5]. Some ATC specimens have components of well-differentiated cancers, but not all (Fig. 16.2) suggesting that ATCs develop from more indolent tumors. Previous reports have shown p53 mutations to be present, and this tumor suppressor likely plays an important role in the pathogenesis of ATC. The TCGA study confirmed a lack of p53 genomic changes in well-differentiated tumors, suggesting that p53 may be a significant driver in addition to other MAPK-related signaling components (Braf, Ras, etc.). More recently, TERT promoter mutations have been identified in high percentage ATCs similar to that of other aggressive cancer types [6]. Thus, it is likely that extensive genomic changes in ATC result in numerous activated molecular pathways that are responsible for driving tumor aggressiveness.

Once a diagnosis of ATC is established, patients should undergo staging workup that includes thyroid function tests and complete blood and chemistry tests. Cross-sectional imaging of the neck, chest, abdomen, and pelvis should be performed. MRI of the neck may have

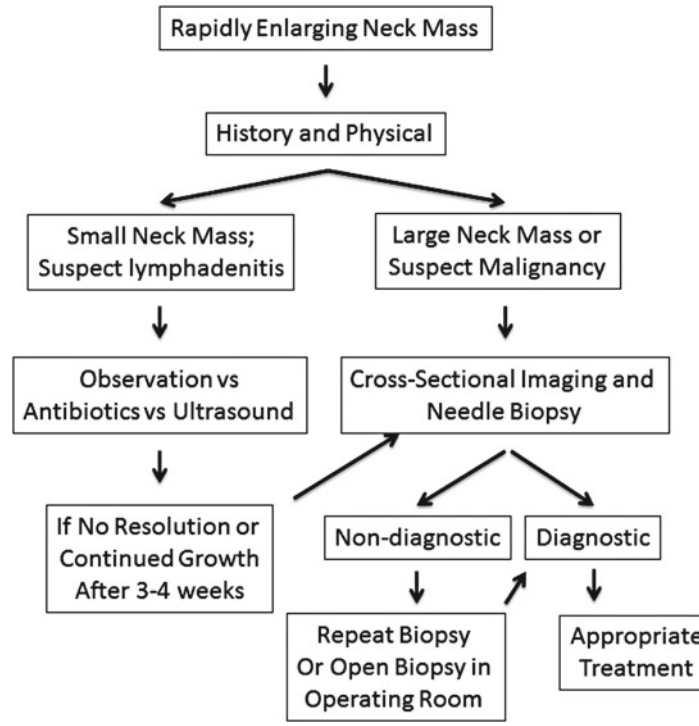

Fig. 16.1 An algorithm for the patient with a rapidly expanding neck mass

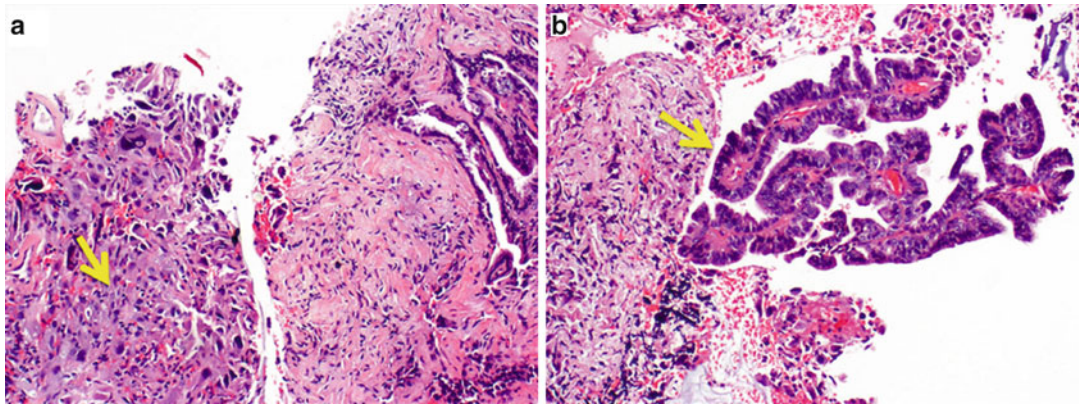

Fig. 16.2 H + E stained slides from a patient with resected anaplastic thyroid cancer. (**a**) Characteristic anaplastic cells without papillary or follicular architecture. The cells have highly irregular shape and heterogenous nuclei (*yellow arrow*). (**b**) The same specimen as in (**a**), demonstrating an adjacent area of tumor that has papillary features (*yellow arrow*)

more advantages over CT in this setting as it can better evaluate tumor invasion of adjacent neck structures. This can be particularly useful in the rare circumstances when resection is being considered. ATCs are highly FDG-PET avid and FDG-PET should be used as a complementary test to cross-section imaging. This is because the presence of distant disease can significantly alter the treatment plan (Fig. 16.3a). In the rare instance where a small, incidental anaplastic thyroid cancer is found after thyroidectomy, FDG-PET and cross-section imaging of the neck and torso can be used to rule out metastatic disease. In addition to these tests, a frank and thorough discussion should be had with the patient and the patient's support structure about the prognosis in ATC. Given that the median survival is measured in months, patients should be prepared for disease progression. The goals of each treatment component (i.e., surgery, radiation, or chemotherapy) should be clearly outlined for the patient with a discussion of expected treatment response and anticipated survival. The natural history of ATC including growth of an unresectable primary tumor and the frequent finding of lung metastases should be described in detail. Discussing symptoms related to disease progression (difficulty breathing, pneumonia, and dysphagia) can help manage the patient's expectations. Having these discussions early can help patients and their families deal with the nearly unavoidable complications that are encountered at the end of life. In this way, palliative interventions (such as feeding tubes and tracheostomy) can be considered by the patient immediately after diagnosis [7]. This is critical so the patient's wishes are honored, particularly if they become unable to make decisions.

It is highly unusual for patients with ATC to have a resectable tumor. More often the tumor invades local structures, such as the carotid artery, the jugular vein, the trachea/larynx, and esophagus (Fig. 16.3b). Margin-negative resection for ATC has been reported in the literature, but these are often small incidental tumors that do not involve local structures [8]. Because of the typical tumor size and local invasiveness, en bloc resections with adjacent organs/neck structures should not be attempted. Previous attempts at resecting extensive tumors have yielded positive gross margins, high morbidity, and no survival benefit [8].

Treatment of ATC generally includes combination regimens of cytotoxic chemotherapy, targeted agents if available, and radiation therapy [9]. Referral to an experienced multidisciplinary group can help guide treatment decisions, as very little data exist comparing the various available regimens [10]. In addition, these groups can facilitate entry into a clinical trial, which is critically important for highly lethal and rare diseases.

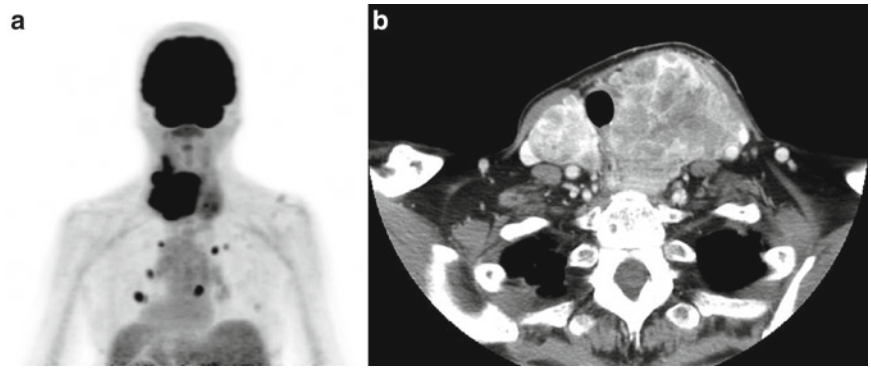

Fig. 16.3 (**a**) PET scan results from a 72-year-old female that presented with a rapidly enlarging neck mass. The mass is hypermetabolic as are multiple cervical and thoracic lymph nodes. (**b**) CT scan of the neck from the same patient from panel A. The tumor occurred in the setting of a long standing goiter and abuts/involves the left carotid artery, jugular vein, esophagus, and fascia

Tracheostomy has been a controversial topic in ATC. Previously, patients with ATC were thought to benefit from immediate placement of a tracheostomy to avoid airway compromise. Given the dismal results with ATC even with tracheostomy, this approach has been reconsidered. ATC often surrounds the trachea and performing a tracheostomy can require dividing part of the tumor. Even when tumor tissue is not divided, ATC is known to grow around and through the tracheostomy creating additional local problems such as bleeding, aspiration, and asphyxiation. For this reason, prophylactic tracheostomy should not be performed in patients with ATC. Instead, a discussion should be had with the patient about the possibility of needing a tracheostomy for symptoms such as dyspnea and stridor in the setting of understanding the potential complications. Thus, tracheostomy should be offered on a case-by-case basis, rather being performed prophylactically in all patients.

Thyroid Lymphoma

Thyroid lymphoma is most commonly a type of B-cell non-Hodgkin lymphoma (NHL). Hodgkin lymphoma of the thyroid is exceedingly rare as are follicular lymphomas and those with a t-cell origin [11]. NHL includes lymphomas originating from natural killer cells or progenitor/mature B and T cells. Patients with NHL can present with a multitude of symptoms. These include cytopenias, electrolyte abnormalities, mass effect on a given organ, fever, and masses in nodal basins or extra nodal locations. Patients with thyroid lymphoma are more often women and present with an enlarging neck mass in their sixth and seventh decade of life. The demographic characteristics are similar to that of ATC.

The principle risk factor for thyroid lymphoma is an antecedent history of Hashimoto's autoimmune thyroiditis. A majority of thyroid lymphoma patients have a thyroiditis component found on histologic evaluation [12]. Why thyroiditis confers a risk for lymphoma is not yet known but may be related to a thyroid immune infiltrate that is exposed to a chronic antigenic stimulation [13].

The two most frequent types of thyroid lymphoma are diffuse large B-cell lymphomas (DLBCL) and MALT lymphoma. DLBCL is the most common accounting for up to 70–80 % of thyroid lymphomas [14]. Two subtypes of DLBCL exist, germinal center and non-germinal center with germinal center being the less aggressive subtype. MALT lymphoma (or mucosal-associated lymphoid tissue) is a more indolent disease than DLBCL, and fewer patients present with disease outside the thyroid [15].

Like ATC, thyroid lymphoma patients can present with large neck mass. The initial work-up includes a thorough history and physical and imaging studies. Diffuse enlargement of the thyroid is more common in thyroid lymphoma as ATC patients more often present with an irregular, one-sided mass. It can present as a painful mass. While fine-needle aspiration cytology is commonly used for evaluation of head and neck masses, this approach does not collect enough tissue for diagnosis and flow cytometry studies. To make systemic treatment decision, including targeted therapies, flow cytometry is used to define the receptor status of a given lymphoma. As such a core biopsy performed in the office using palpation or ultrasound to guide the needle is easily obtained and well tolerated. Two to three passes with a core biopsy is typically enough material for H+E, immunohistochemistry, and flow cytometry. Open biopsy can also be performed if there is difficulty in achieving a diagnosis, but with image guided biopsy approaches this is rarely needed.

Once thyroid lymphoma has been diagnosed, staging studies are needed to determine the extent of disease. CT scans of the head and neck, chest, abdomen, and pelvis along with whole body PET scan are adequate for staging (Fig. 16.4a, b). The most commonly used staging system for lymphoma is the Lugano modification to the Ann Arbor staging classification. Stage IE (E stands for extranodal) disease is a single extranodal lesion without nodal involvement; stage IIE includes nodal involvement on the same side of the diaphragm. Stage III and IV include those with nodes on both sides of the diaphragm or other non-lymphatic involvement, respectively.

Similar to ATC, thyroid lymphoma patients can have compression of the trachea, larynx, and esophagus resulting in difficulty breathing, stridor, and dysphagia. Depending on the size of the lymphoma, patients should be counseled about the potential need for tracheostomy and gastrostomy. As in ATC, these decisions to palliate symptoms should be made by the patient together with the surgeon and medical oncologist. While there are certainly more effective systemic agents for thyroid lymphoma as there are for ATC, the goals and expectations of the intervention should be plainly and thoroughly discussed with the patient.

Treatment approaches to thyroid lymphoma have been controversial. Initial reports of surgical resection and debulking suggested these as potentially useful strategies. However, contemporary practice has successfully incorporated systemic treatments and radiotherapy with excellent long term controls rates. Surgery should have a very limited role in the treatment of thyroid lymphoma. Previous attempts at debulking/resection in combination with radiotherapy did not demonstrate an improvement over radiotherapy alone [16, 17]. The success of modern chemotherapy and radiotherapy regimens has solidified their use as first line treatment in thyroid lymphoma. For DLBCL, typical regimens include CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) plus Rituximab if CD20 is positive (Fig. 16.4c). Radiotherapy can follow systemic treatment.

MALT lymphoma is treated with surgery only when incidentally noted on pathology specimens after thyroidectomy. If this is the only disease that was present (stage IE), then surgery is all that is needed as survival is 100 % at 7 years [13]. In theory, if a stage IE MALT lymphoma was diagnosed after work-up of a thyroid nodule, then it could be managed with thyroidectomy. However, local control rates are excellent with radiotherapy alone and is recommended for treatment of disease limited to the thyroid [11]. For disease outside the thyroid, radiotherapy plus systemic treatment should be considered.

Disease-specific survival rates have been published from the SEER database in a study of 1408 patients. As expected, DLBCL patients have shorter survival than MALT lymphoma patients [14]. DLBCL had a 5-year-disease-specific survival of 75 % while MALT lymphoma was 96 %.

Metastases to the Thyroid Gland

At autopsy, up to 25 % of patients with a known malignancy will have metastases in the thyroid [18]. However, patients presenting with

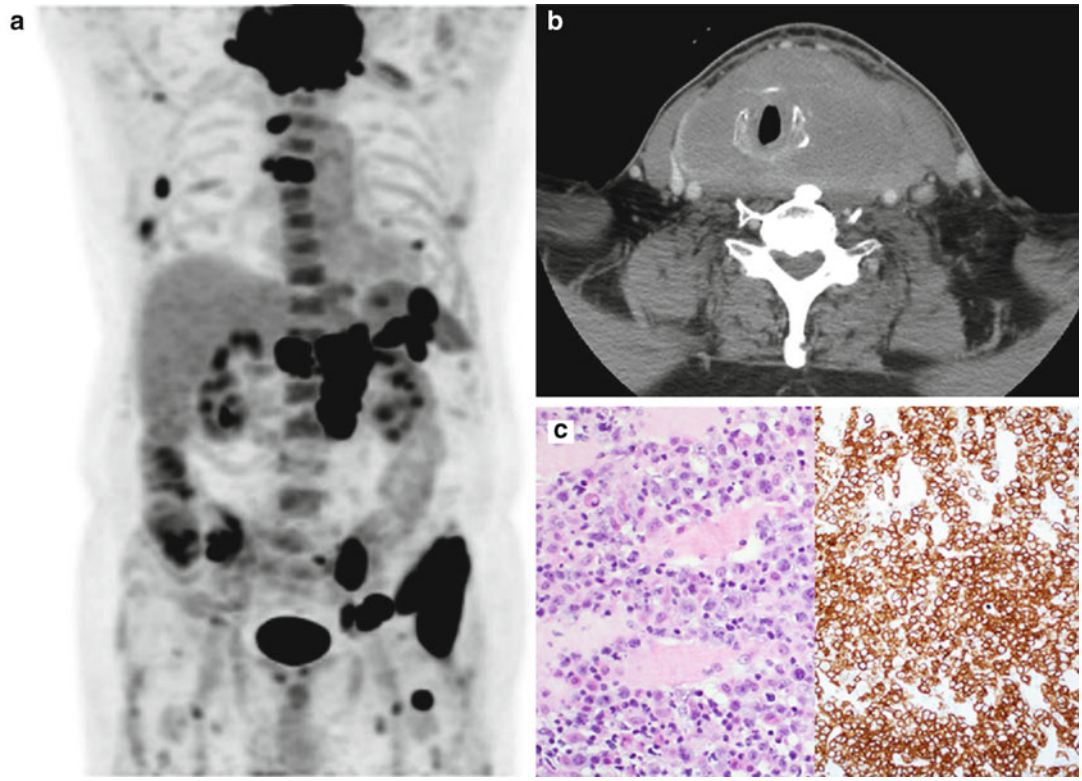

Fig. 16.4 A newly diagnosed patient with thyroid lymphoma. (**a**) PET scan demonstrating enlarged thyroid with intense hypermetabolism with similarly avid lesions in the cervical, thoracic, retroperitoneal and pelvic lymph nodes. Additional lesions can be seen in the spleen, adrenal, and bone marrow. (**b**) CT scan of the neck demonstrating homogenous enlargement of the thyroid gland. (**c**) *Left panel* is an H+E of a core biopsy performed on the mass and shows sheets of large pleomorphic cells with irregular nuclei, prominent nucleoli, and moderate amount of cytoplasm. *Right panel* is immunohistochemistry staining for the B-cell surface marker CD20. This patient was diagnosed with diffuse large B-cell lymphoma, non-germinal center B-cell phenotype

metastases to the thyroid is very rare. The most common presentation is an incidental mass on exam and less frequently by imaging [19]. Surveillance imaging after malignancy treatment can detect thyroid lesions that are then referred to the physician for further work-up [20]. Common malignant histologies that are found in the thyroid include renal cell carcinoma, melanoma, breast and lung cancer, and colorectal carcinoma [21]. As with any neck mass or thyroid lesion, a full evaluation of the patient and imaging is critical for making management decisions. FNA has an excellent yield for making a diagnosis for routine thyroid or head and neck masses. The most cost-effective approach to work-up is to begin with a bedside/clinic ultrasound and an FNA biopsy. Further work-up can then be based on cytology results. Pathology assessment in these cases can be challenging and when possible, the pathologist should be alerted to the possibility of a metastatic lesion.

Once the histologic origin of the metastasis has been determined, clinical management depends on a number of factors. If the patient has no history of the malignancy, then further work-up and imaging should focus on identifying the primary tumor. If the patient has a history of the malignancy then further work-up (such as cross-sectional imaging and FDG-PET) should be performed to determine if there are additional sites of metastatic disease.

Very little data exists to help guide treatment decisions in this situation. Outcomes after metastasectomy from any organ site are difficult to

interpret because of the selection bias that is used to choose patient for resection [22]. Fit patients with longer disease-free intervals are more likely to be offered resection by the surgeon than patients with synchronous primary tumor and metastases or those with short disease-free interval after a primary tumor resection. For this reason, most decisions to perform metastasectomy should be done in a multidisciplinary fashion with physicians that are experienced in treating a given malignancy. Disease-free intervals, malignancy aggressiveness, and other organ involvement are all variables that can affect patient management, which might include systemic treatment, watchful waiting, or metastasectomy.

While the benefit of metastasectomy has not been proven, it is reasonable to offer patients resection if they have isolated disease. Conversely, patients with aggressive and widespread disease who have a poor prognosis do not require intervention, as their survival will ultimately be determined by their extensive disease burden. For those with isolated disease, there are several important thyroid-specific considerations. Because tumors within the central compartment can affect neck structures (such as the trachea, the recurrent laryngeal nerve, and the esophagus), the risks of operation should weighed carefully against the risks of nonoperative management [23]. For example, an intrathyroidal tumor that can be managed with a lobectomy may be a reasonable candidate for metastasectomy, even if there is a short disease-free interval or if other metastatic disease is present. This approach is to avoid complications of growth in the central compartment. In select patients, there may be a "window" for a relatively straightforward resection that closes if the tumor becomes too large or invades other structures.

Conclusions

Anaplastic thyroid cancer, thyroid lymphoma, and metastases to the thyroid are rare thyroid tumors. Thyroid physicians should be familiar with the various management strategies and appreciate that the lack of well-designed studies to help guide decision making particularly for ATC and metastases to the thyroid. Particularly for ATC, clinical trial enrollment is needed to improve outcomes.

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17 The Role of Targeted Therapies or Nonsurgical Treatment of Thyroid Malignancies: Is Surgery Being Replaced?

Daniel C. McFarland, Indu Varier, and Krzysztof Misiukiewicz

Abbreviations

Akt	Also known as protein kinase B
Braf	v-raf murine sarcoma viral oncogene homolog B11 DNA, deoxyribonucleic acid
ERK	Extracellular signal-regulated kinases
HDAC	Histone deacetylase inhibitor
Mek	Mitogen-activated protein kinase
mTOR	Mammalian target of rapamycin
PI3K	Phosphoinositide 3-kinase
Ras	Rat sarcoma proteins
RET TKR	Rearranged during transfection tyrosine kinase receptor
TKR	Tyrosine kinase receptor
VEGFR	Vascular endothelial growth factor receptor

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Introduction

Historically, the treatment of thyroid cancer has been surgical, and additional nonsurgical modalities were limited to adjuvant radioiodine ablation and external beam radiation. Chemotherapy would be considered only in relapsed, refractory, or particularly aggressive cases. Targeted therapies are changing this paradigm. Thyroid cancer mutational drivers are being quickly elucidated, and rationally directed treatments have had encouraging successes with limited toxicity, not seen with other medical treatments in thyroid cancer previously. Thyroid cancer is on the forefront of personalized medicine due to the array of thyroid cancer mutational signatures and their hereditary propensity. However, many key questions remain to be answered. There are still limited complete responses and the best use of the currently available agents has not truly been discovered. Thus, genuine personalization is on the horizon but not yet a reality; we cannot yet predict treatment responses based on genetic mutations. The inevitable elucidation of thyroid cancer biology and rational treatments means that for the minority of patients who were not cured with surgery, there is hope for long remissions and even cures.

The nonsurgical modalities for thyroid cancers are localized external beam radiation or systemic treatment with radioactive iodine (RAI) ablation, TSH suppression, cytotoxic

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chemotherapy (e.g., doxorubicin, cisplatin, or dacarbazine), or the newly approved multityrosine kinase inhibitors such as sorafenib and lenvatinib for differentiated thyroid cancers (DTC) or vandetanib and cabozantinib for medullary thyroid cancers (MTC).

This chapter will provide a general overview of the standard nonsurgical treatments of thyroid cancer and focus particularly on evidence for targeted therapy paradigms, experimental (but clinically applicable) single or multi-agent therapies, radiosensitizing agents, and redifferentiation strategies for radioactive iodine-resistant (RAI-R) metastatic well-differentiated thyroid cancer (DTC) cases. The chapter will address the most common types of well-differentiated thyroid cancers (e.g., papillary and follicular), particularly RAI-R DTC, as well as the neuroendocrine variant of thyroid cancer, medullary thyroid cancer (MTC). Anaplastic and poorly differentiated thyroid cancers will be addressed peripherally. This chapter will conclude with a series of four theoretical cases that bring up controversial issues where experimental chemotherapy, novel targeted agents (i.e., tyrosine kinase inhibitors), and combinations of routine modalities could potentially be utilized in unique ways.

Natural History of Thyroid Cancers

Thyroid cancers have distinct behaviors based upon four main types of histology (papillary, follicular, medullary, and anaplastic or dedifferentiated thyroid cancers) and upon mutational analysis (most commonly BRAF (40–45 %), RET (10–20 %), RAS (10–20 %) [1]. Mutations can either be hereditary or acquired, and they tend to accumulate as tumors become progressively more dedifferentiated and respond less well to systemic agents (radioiodine ablation, chemotherapy). Thyroid cancers are heavily represented among cancers that involve germline mutations (typically 5–10 %), particularly the RET/PTC mutations in medullary thyroid cancers (MTC), but the majority of associated mutations are sporadic in nature. The vast majority, about 93 %, is considered differentiated thyroid cancers (DTC), which include papillary (PTC), follicular (FTC), and Hürthle cell thyroid carcinoma (HTC) subtypes. These indolent types are usually found incidentally or present as a thyroid nodule. The more aggressive-behaving subtypes are MTC and anaplastic thyroid cancers (ATC) and represent 4–6 % and 2 % of all thyroid cancers, respectively. MTC and ATC may quickly become symptomatic, require prompt treatment, and present unique treatment dilemmas. Although approximately 90 % of indolent well-differentiated subtypes (i.e., PTC, FTC) are cured with surgery as the primary treatment modality, 3–15 % will present with distant metastasis and another 6–20 % will develop distant metastasis during follow-up [2]. Even with distant metastasis, DTC is still considered an indolent cancer with a good prognosis if remission can be achieved with radioiodine [3]. However, the prognosis worsens significantly if it loses its radioiodide avidity, which happens in roughly 30–50 % of metastatic cases [4]. The 5-year survival rate of a patient with iodine-concentrating pulmonary metastasis declines from between 60 and 80 % to around 30 % once the tumor no longer takes up iodine [4]. For these recurrent, refractory, or metastatic patients, nonsurgical modalities play an integral role in treatment.

Prognosis

A lack of clear guidelines delineating when to initiate medical treatment for thyroid cancer is a challenge in the medical management of thyroid cancer. Different staging systems are available, but a standard prognostic tool that incorporates mutational status has not been discovered, and there is not agreement about when to start various medical therapies. Ten-year overall survival rates are as high as 85 % in patients under 60 years old with no extension beyond the thyroid capsule and no local or distant metastasis [5]. Thyroid cancer is the only cancer type that uses age as part of the staging criteria for well-differentiated types [6, 7]. Histology also plays a strong role in staging and prognostication [8, 9]. Numerous factors provide for a less advantageous prognosis, including older age, larger thyroid tumor, extension beyond the capsule, lymph node involvement, aggressive

tumor histology, macroscopic vascular invasion, lack of radioactive iodine uptake (RAIU) [18], fluorodeoxyglucose PET positivity, as well as BRAFV600E and other mutations associated with dedifferentiation [10]. Rates of survival are significantly decreased with less advantageous subtypes. Additionally, any diagnosis of ATC is automatically stage IV given its incurability.

Several risk stratification systems exist for thyroid cancers based on the likelihood of disease-specific death after the initial diagnosis. The most commonly used tumor node metastasis (TNM) staging system is promulgated by the American Joint Committee on Cancer (AJCC). There is also the metastasis, age, completeness of resection, invasion, and size (MACIS) and the age, metastasis, extent of disease, and size (AMES) categorization systems for staging that are limited to papillary thyroid cancers. Age is a common component to each system, denoting more advanced stage and higher all-cause and cancer-specific mortality [8, 11–15]. Besides age, historically, other factors such as gender, lymph node involvement, and serum TSH concentrations are used to prognosticate and guide therapies. Females have better outcomes than men and this may be due to more aggressive subtypes in men, but there is not definitive evidence and it is a controversial assertion that should not be used to guide treatment. Local lymph node involvement (i.e., metastatic cervical lymph nodes) is frequently seen in locally advanced disease (i.e., up to 90 % of patients will have micrometastatic disease) in PTC. A SEER-based retrospective analysis has been shown to impact disease outcomes when combined with age (i.e., over 45 years old) in PTC [16]. Higher risk of mortality is seen in both age groups in FTC with cervical lymph node involvement. Recently, lymph node ratio has been shown to be an independent prognostic marker in PTC when used with existing staging systems [17]. Successful TSH suppression has been shown to improve prognosis in high-risk DTC patients [18], and TSH concentration is associated with risk of cancer in a thyroid nodule [19–21].

Molecular markers are beginning to show prognostic discriminative ability that is particularly important in otherwise low-risk disease. To date, the most meaningful of which has been $BRAF^{V600E}$ that, when present, will predict for a 20 % cumulative PTC recurrence at five years over the baseline PTC recurrence of 8 % with BRAF wild type [22]. $BRAF^{V600E}$ is significantly associated with time to recurrence when added to the AMES, MACIS, AJCC/TNM, and ATA recurrence-risk category. In contrast to the BRAF mutation, RAS mutations and RET/PTC rearrangements, which are also common genetic alterations in PTC, are much less commonly associated with aggressive pathogenesis [23].

Standard Nonsurgical Treatment of Thyroid Cancers: Adjuvant Treatments

Locally advanced thyroid cancer after total thyroidectomy is most frequently treated adjunctively with RAI ablation therapy in order to eliminate macro- and microscopic metastatic disease. RAI therapy additionally serves the function of assessing for additional evidence of metastatic disease and can be used at doses from 100mc to 200mc. Additionally, TSH suppression with levothyroxine can be used in both the localized and metastatic setting to suppress the activity of any remaining thyroid cancer. This modality is typically limited by the side effects of ongoing TSH suppression such as thyrotoxicosis, palpitations, weight loss, and cardiovascular risk. It can be used intermittently and at the discretion of the endocrinologist, as there is not a strict standard of care (NCCN guidelines). There is also no consensus regarding the definition of RAI, nor is there a true consensus regarding inclusion or exclusion criteria or treatment guidelines [24]. RAI ablative therapy is not standard in MTC. However, although C cells do not concentrate iodine, the iodine is toxic to C cells, and therefore, it is minimally effective [25].

In general, results of adjuvant RAI are not satisfactory. Options for redifferentiation of thyroid cancer cells are ongoing, and other novel ideas such as combinations with targeted therapies or chemotherapy or use as maintenance therapy are forthcoming [26].

Monitoring for Progression

After effective adjunctive RAI, radioactive iodine scan can be used to monitor for progression of disease and as an additional treatment modality with variable dosing. Serum thyroglobulin, which is present in normal thyroid tissue, can be used as a tumor marker to assess for progression of disease. In general, thyroglobulin is not a reliable marker that will indicate when to initiate treatment. For example, it is not effective if the patient has antithyroglobulin antibodies at baseline since the antibody will preclude an accurate assessment of residual and/or growing thyroid tissue. Titers of antithyroglobulin antibodies can be followed to assess for progression of disease as a rising anti-TG titer indicates progression of disease. A threshold level for when to initiate treatment using either thyroglobulin or an anti-TG titer is not available or standardized which means that both markers are not consistent and reliable and neither determines when to initiate treatment.

Despite recent improvements in care for thyroid cancers with rationally based targeted agents, a perfect biomarker for evaluating disease is not currently available.

Role of Chemotherapy

Although chemotherapy has a limited, albeit established, role in the metastatic setting of differentiated thyroid cancers, its use as a treatment modality in postsurgical adjuvant settings is virtually nonexistent. Even in metastatic settings, doxorubicin the only FDA-approved chemotherapy for DTC offers little to no benefit and is associated with significant toxicity. Selected chemotherapeutic trials in thyroid cancers are listed in Table 17.1.

Table 17.1 Select studies with cytotoxic agents

Author and year	Drug dose/trial design	Thyroid CA type	Responses	Safety and observations
Gottlieb 1972 [27]	Various single and combination agents (observational)	"Spindle cell and giant cell carcinoma" 16, MTC 13, other 8. Total $n=37$	– Median duration of response 3 months – Five of 37 patients had PR – Three of the five responders received doxorubicin	Encouraging results with doxorubicin
Gottlieb 1974 [28]	Doxorubicin 45–75 mg/m^2 q 3 weeks/cohort observational	Various, $n=30$	– Eleven patients had >50 % decrease in tumor size	
Kim 1983 [86]	Doxorubicin 10 mg/m^2 weekly and RT (200 rad fractions) daily × 5.5 weeks/cohort	Locally advanced differentiated carcinoma (mixed PTC/FTC) $n=10$	– Seven of eight evaluable patients had complete tumor regression	Acute reactions were confined to radiation fields
Shimaoka 1985 [31]	Doxorubicin 60 mg/m^2 IV q 3 weeks versus doxorubicin 60 mg/m^2 IV q 3 plus cisplatin 40 mg/m^2 q 3 weeks	Various $n=41$ single agent, $n=43$ combination	– No overall response difference – 17 % RR single agent and 26 % RR combination – Five CRs were seen in the *combination* group and none in single-agent group	• Greater toxicity in combination group (5 vs. 2 life-threatening toxicities) • Notable CR in combination group

(continued)

Table 17.1 (continued)

Author and year	Drug dose/trial design	Thyroid CA type	Responses	Safety and observations
Williams 1986 [30]	Doxorubicin (60 mg/m^2) plus cisplatin (60 mg/m^2)	Advanced thyroid cancer, $n=22$	2 brief PR (9.1 %)	One drug-related death
Scherübl 1990 [106, 107]	Doxorubicin 50 mg/m^2 + cisplatin 60 mg/m^2 + vindesine 3 mg/m^2/ single-arm observation	Progressive DTC and MTC $n=20$	– One PR (MTC), three SD of the 18 evaluable patients (10MTC, 8 DTC)	Combination—not superior to single-agent doxorubicin. One episode of cardiomyopathy
Leaf 2000 [108]	Etoposide 140 mg/m^2 daily for 3 days every 3 weeks until progression	Progressive RAI-R DTC	– No responses among ten patients accrued	Two grade 4 leukopenia and a grade 5 leukopenia
Ain 2000 [109]	Paclitaxel 120 mg–140 mg/m^2 96-h infusion q 3 weeks × 6 cycles/ prospective phase II	Anaplastic $n=20$	– 53 % total response rate (CI 29–76 %) with 1 CR, 9 PR of 19 evaluable participants	No toxicities greater than grade 2
Santini 2002 [33]	Carboplatin 300 mg/m^2 and epirubicin 75 mg/m^2 every 4–6 weeks for six cycles and TSH stimulation achieved by reduction of L-thyroxine or administration of recombinant human TSH	Progressive RAI-R DTC with lung metastasis $n=14$	– Overall positive response was 37 % (81 % including SD). One CR, five PR, seven SD – Serum thyroglobulin declined 50 % in six patients	Toxicity requiring withdrawal from study in two patients (cytopenias)
Matuszczyk 2008 [29]	Doxorubicin 15 mg/m^2 weekly × 8 cycles or 60 mg/m^2 q3 weeks × 3 cycles/retrospective cohort	Progressive FTC or MTC $n=22$	5 % PR, 42 % SD, 53 % PD. Less PD for DTC treated with q3 week regimen	Doxorubicin was well tolerated in both groups
Crouzeix 2012 [82]	Doxorubicin 60 mg/m^2 with cisplatin 40 mg/m^2 every 4 weeks for 6 cycles. Paclitaxel 175 mg/m^2 with carboplatin 5 AUC every 4 weeks for 6 cycles	Progressive RAI-R DTC after TKIs (vandetanib, sorafenib, sunitinib) $n=1$ (i.e., progression 3 months after vandetanib, 4 months after sorafenib and SD with sunitinib)	– CR to doxorubicin-cisplatin lasting 10 months – CR to paclitaxel-carboplatin lasting 5 months	Grade 3 alopecia, grade 2 neuropathy
Besic 2012 [34]	Neoadjuvant treatment from 1979 to 2004	FTC or HCTC T3 or T4. Mean tumor diameter 9.3 cm. Extrathyroid growth in 15 patients and regional/distant metastasis in 6 and 12 patients, respectively	– Tumor size decreased by >50 % in 13 patients (45 %) and response varied based on distant metastasis (17 %) or not (65 %)	R0, R1, R2 resections were performed in 15, 10, and 4 cases, respectively
Besic 2013 [35]	Neoadjuvant treatment from 1988 to 2005 (vinblastine 11 cases, vinblastine + doxorubicin 2 cases, other 3 cases)	Variants of aggressive PTC $n=16$, mean tumor diameter 9.67 cm	– Tumor size decreased in all; by >50 % in 7 (44 %) and <50 % in 9 patients	R1, R0, and R2 resections performed in 2, 10, and 4 cases, respectively

AUC area under the curve, *CI* confidence interval, *CR* complete response, *DTC* differentiated thyroid cancer, *FTC* follicular thyroid cancer, *HCTC* Hürthle cell thyroid cancer, *MTC* medullary thyroid cancer, *PTC* papillary thyroid cancer, *PR* partial response, *RAI-R DTC* radioiodine ablation refractory DTC, *SD* stable disease

Early case reports from the 1960s of patients diagnosed with thyroid cancer did not describe therapeutic regimens in sufficient detail and represented an inadequate methodological approach to cancer research. In response to this gap of knowledge in thyroid cancer research, Gottlieb et al. summarized 37 case reports of patients with thyroid cancer, who were treated at the MD Anderson Hospital and Tumor Institute with various chemotherapeutic agents given alone or in combination [27]. These case reports involved different histologic types of thyroid cancer, such as medullary, Hürthle cell, papillary, and follicular carcinoma. Six out of the 37 patients had DTC. Doxorubicin was administered to all patients at 60–75 mg/m2 IV either as a single dose or divided into three consecutive doses. Only 5 out of the 37 patients had partial remission of the disease, and three of those five responded to doxorubicin. The median duration of the responders was only 3 months.

Considered encouraging at the time, doxorubicin gained popularity, and results from previous study involving this drug led to a prospective clinical trial studying 30 patients with thyroid cancer. Therapy with doxorubicin at three different dosing levels (75, 60, or 45 mg/m2 IV) repeated at 3-week intervals was given until progression or toxicity that precluded further drug administration [28]. Cardiomyopathy was associated with high cumulative doses of doxorubicin, and as a result, the total dose of doxorubicin delivered was subsequently limited to 550 mg/m2. Partial remission was seen in 11 patients. Among the 11 responders, five patients had papillary-follicular or Hürthle cell, three had medullary, two had spindle and giant cell, and one had an unclassified carcinoma. Patients showing an objective response lasting for at least one month were classified as having achieved a partial remission if they had a 50 % or greater decrease in the product of the largest perpendicular diameters of all measurable lesions without a simultaneous increase in the size of any lesion or the appearance of any new metastases. The lowest dose level (45 mg/m^2) was the least effective, and the 60 mg/m^2 and 75 mg/m^2 dose levels appeared to be identical in response rates. This study, characterized by a small sample size, various histologic types, and different dose levels, did not generate innovative results, but it warrants further studies.

The assumption that doxorubicin may not be efficacious has not been confirmed in multiple, larger, and better designed studies reported over the past 30 years. Typically partial responses of brief duration were observed in 5–15 % of patients and were associated with significant toxicities. In 2007, Matuszczyk et al. reported a retrospective study with doxorubicin given at two different dose levels: 60 mg/m^2 over 3–6 cycles every 3 weeks or 15 mg/m^2 over 8–16 cycles with maximum dose limited to 550 mg/m^2 [29]. The efficacy of the chemotherapy was evaluated by radiographic imaging (FDG-PET and bone scans) using the WHO criteria performed 4 weeks after the completion of the last cycle of chemotherapy. In patients with papillary or follicular thyroid carcinoma, 5 % had partial regression over 6 months, 42 % had stable disease for a median of 7 months, and 53 % had disease progression. Studies conducted in the 1970s and 1980s led to the commonly held assumption that palliative doxorubicin would induce a time-limited response rate of around 30 %. However, recent data by Brose et al. demonstrated that the overall response rate was most likely overestimated due to the outdated CT imaging and the lack of RECIST criteria and that the actual overall response rate of any chemotherapy was closer to only 5 % [10].

Given the limited efficacy of monotherapy regimens, doxorubicin-based combination chemotherapies have been tested in clinical trials. Williams et al. from the Southeast Cancer Study Group reported 22 evaluable patients with all histologic types of advanced thyroid cancer [30]. Patients were treated with doxorubicin 60 mg/m^2 and cisplatin 60 mg/m^2, and only two brief partial responses were observed (9.1 %). In addition, treatment was associated with considerable toxicity, including one treatment-related death. Surprising results were seen in a study by Shimaoka et al. with the same combination but dosed at 60 mg/m^2 for doxorubicin and 40 mg/m^2 for cisplatin given every 3 weeks [31]. Patients

were randomized to the combination versus to doxorubicin alone. Among a group of 35 patients with DTC, complete and partial responses observed in combination versus monotherapy were 16 % (3/19) and 31 % (5/16), respectively. Other combinations showed similar results. Matuszczyk et al. examined the combination of paclitaxel and gemcitabine in advanced DTC. No responses were observed among nine patients, who had continuously progressive disease at the time of response assessments and experienced toxicity such as hair loss (100 %), respiratory infection/pneumonia (32 %), neutropenia (11 %), and peripheral neuropathy (11 %) [32]. In anticipation to enhance chemotherapy's effect with thyroid-stimulating hormone (TSH) stimulation, a combination of epirubicin and carboplatin following exogenous or endogenous elevation of TSH was tested. Since chemotherapy cytotoxic activity is higher in rapidly proliferating cells, TSH was given to stimulate tumor cell growth. Among 16 patients, 1 (6 %) had a complete response (CR), 5 (31 %) had a partial response (PR), and 7 (44 %) had stable disease (SD) [33].

Neoadjuvant chemotherapy has been shown to convert an inoperable tumor to an operable mass and thus improve a patient's prognosis. An interesting study from Slovenia, where incidence of goiter, FTC, and HTC was noticed, reported a retrospective and nonrandomized study with patients who had T3 or T4 tumor and were treated with neoadjuvant chemotherapy from 1979 to 2004 [34]. Mean tumor diameter was 9.3 cm and extrathyroid growth was seen in 15 patients. Chemotherapy given was often started with the least aggressive schedule, and if necessary, more aggressive schedules were used. Treatment consisted of vinblastine in 19 cases, vinblastine with doxorubicin in five cases, or other regimens in five cases. Successful tumor resection after chemotherapy was performed in all patients, but R0, R1, R2 surgeries were done in 15, 10, and 4 cases, respectively (R0 defined as no residual tumor, R1 as microscopic residual tumor, and R2 as macroscopic residual tumor). Neoadjuvant chemotherapy was effective in patients with FTC and HCTC in 47 % and 43 %, respectively.

The same group reported that neoadjuvant chemotherapy for papillary thyroid cancer may be effective in 44 percent of patients [35]. With 16 patients treated between 1988 and 2005, the median tumor diameter was 9 cm and excessive thyroid tumor growth was present in 13 surgical specimens. Similar to previous studies, chemotherapy consisted of vinblastine only in 11 cases, vinblastine with doxorubicin in two cases, or other regimens in three cases. All patients underwent thyroidectomy and R0 was done in two, R1 in 10, and R2 in four patients. Also worth mentioning, a preoperative and/or postoperative external irradiation was performed in 75 % of patients.

Mutational Basis for Targeted Therapies

As opposed to the non-discriminant cell kill of cytotoxic chemotherapy, targeted therapies are rationally based on specific genetic properties of individual tumors. Thyroid cancers harbor one of the most fascinating models of carcinogenesis. The past 25 years have brought many newly described genetic lesions to light that are associated with various types of thyroid cancer [36]. In DTC, two primary signal transduction cascades, the PI3 kinase and MAP kinase pathways, accumulate increasingly activating mutations as they become more dedifferentiated and aggressive [1]. Anaplastic thyroid carcinoma (ATC) commonly displays mutations in RAS and BRAF as well as TP53 and PIK3CA and/or AKT mutations. Medullary thyroid carcinoma (MTC) is associated with RET mutations in virtually all hereditary cases and about half of sporadic cases. As driver and passenger mutations are increasingly understood, targeted agents, in particular the tyrosine kinase inhibitors, hold much continued promise in the treatment of metastatic well-differentiated thyroid cancer, perhaps even in combination with each other. These agents are rationally based on targeting signaling transduction pathways that are aberrantly activated in thyroid cancers [37]. These overly active signal transduction pathways

(PI3 kinase-AKT, Ras pathways) may be associated with either germline or sporadic mutations.

Papillary thyroid cancer (PTC), which is the most common form of well-differentiated DTC, features a range of genetic alterations in the PI3 kinase and MAP kinase pathways, all of which result in the activation of RAF/MEK/ERK signaling. Of these genetic lesions, the most common is the notable V600E mutant of BRAF, also found in other cancers, most typically melanoma and colorectal cancers. Treatment implications are most pronounced for melanoma where deep responses are seen in BRAFV600E-mutated patients with the BRAF inhibitor vemurafenib but have not been seen in BRAFV600E-mutated colorectal cancers. The Cancer Genome Atlas (TCGA) program recently completed a comprehensive genomic analysis of approximately 500 PTC and confirmed prior studies regarding the frequency of key driver mutations in PTC: BRAF 57 %, *RAS* 12 %, and fusion oncogenes (*RET/PTC*, *NTRK1*, others) 9 % which are all mutually exclusive [38]. In total these mutations that result in dysfunctional ERK signaling account for approximately 70 % of PTC [39, 40]. BRAF itself is seen in at least 38 % of PTC and is also found in poorly differentiated and anaplastic thyroid carcinomas with a prevalence of 12 % and 50 %, respectively [41, 42]. These genetic mutations are mutually exclusive and suggest the importance of RAF/MEK/ERK signaling in PTC. Ample evidence suggests that thyroid cancers are dependent on constitutive cellular oncogenic drivers similar to the oncogene prototype, chronic myelogenous leukemia (CML). Similar to CML, thyroid cancers retain viability based on the constitutive activity of the oncogenic driver that was responsible for tumor development. A resistance model can be extrapolated from the BCR-ABL oncogene of CML where additional driver mutations are developed as the tumor becomes more resistant. Resistance in thyroid cancer can be seen as loss of differentiation and iodine uptake function that is specifically seen with BRAFV600E mutations that confer the loss of radioiodine concentrating ability. Acquired resistance to RAF and MEK inhibitors is also seen in BRAF mutant thyroid cancers.

The sodium-iodide symporter (NIS) is responsible for the uptake of iodine into thyroid cells and is required for the uptake of therapeutic ^{131}I into thyroid cancer cells. A significant and sustained downregulation of the NIS is a primary effect of RAF/MEK/ERK signaling pathway activation that directly impacts the efficacy of RAI therapy. Expression of NIS (as well as other genes typical of differentiated thyroid cells) is suppressed by activation of RAF/MEK/ERK [43]. An analysis of tumor samples for NIS expression indicates a relative loss of NIS expression as well as the expression of other thyroid-specific genes relative to normal thyroid tissue [44, 45]. Further, NIS expression is lower in BRAF mutant tumors than in those without BRAF mutation [44, 46]. The thyroid-specific BRAFV600E mutation revealed the suppression of NIS expression, thyroid peroxidase (TPO), thyroglobulin (Tg), and blockade of ^{124}I uptake, all of which were reestablished once expression of oncogenic BRAF is turned off. The genetic or pharmacological blockade of the pathway restores their expression and consequently their ability to incorporate iodine into tyrosine (iodine organification), which is associated with greater retention time of ^{131}I in cancer cells [47].

Other MAPK-activating alterations common to thyroid cancer can also cause dedifferentiation. MEK inhibitors have been shown to restore thyroglobulin and thyroid peroxidase expression in RET/PTC thyroid cancer cells [48, 49]. Data are consistent with the hypothesis that activation of MEK, regardless of the upstream-activating mutation, is a key factor in the loss of thyroid differentiation-specific gene expression including NIS [48]. Both an unselected and a genetically selected population may benefit from treatment with a combination of MEK inhibitor, and RAI as a MEK inhibitor may facilitate the delivery of greater RAI treatment effect but remains to be satisfactorily studied.

Introduction of Targeted Therapies

Tyrosine kinase inhibitors now represent the second, third, and fourth FDA-approved agents for thyroid cancers in the last 3 years. Vandetanib

was approved in 2011 and cabozantinib was approved in 2012 for the treatment of metastatic MTC. Sorafenib was approved in 2013 for the treatment of metastatic DTC. Lenvatinib was found to extend PFS (OS not reached) in RAI-R DTC in the phase III SELECT trial representing an addition to the targeted therapy in RAI-R DTC but has not been approved by the FDA at the time of this writing. These agents successfully halt the progression of disease but are less successful in inducing absolute tumor shrinkage, and there is no evidence that they prolong survival. All of the most successful agents are multikinase inhibitors. Studies that led to FDA approvals are presented in Table 17.2. The mechanism and sites of action are demonstrated in Fig. 17.1.

Vandetanib (ZD6474) is an orally administered TKI that inhibits VEGFR, EGFR, and RET signaling pathways [50] and is FDA approved for the treatment of metastatic MTC. It has a median T_{MAX} of 6 h (fasting) and 8 h (after food ingestion) [50] and a terminal half-life of 8–18 days. It is highly protein bound and accumulates in severe renal failure. It takes 2 months to achieve a steady-state concentration. Wells et al. (2012) tested vandetanib in a randomized fashion using 300 mg daily in 331 patients with advanced MTC (231 to vandetanib, 100 to placebo) with a median follow-up of 24 months [51]. The study met its primary objective of PFS prolongation HR 0.46, CI 0.31–0.69, $p<0.001$. Disease control (e.g., stable disease SD) ($p=0.001$) and biochemical response (e.g., thyroglobulin) ($p<0.001$) end points were also met. The primary side effects were GI. Approximately 50 % of the patients receiving vandetanib had a dose reduction or interruption compared to 15.2 % in the placebo group (Wells) [51]. The reason for withdrawal was due to AEs in 12.1 % of vandetanib patients and 3 % of placebo patients or disease progression (30.7 vandetanib vs. 55 % placebo). The most common AE reported leading to treatment discontinuation was GI (3.0 % total patients discontinued due to GI reason) (e.g., diarrhea, dysphagia, nausea, pancreatitis, peritonitis, small intestinal perforation, and vomiting). Asthenia, fatigue, skin disorders, photosensitivity reactions, QTc prolongation, elevated creatinine, and hypertension were also associated with discontinuation. Cardiac disorders such as hypertension and QTc prolongations were significantly associated with vandetanib versus placebo. It is also associated with increased levels of parathyroid hormone. Overall, vandetanib has proven efficacy over placebo in advanced MTC but has significant toxicity (GI and cardiac). It is not known if the mechanism of action is purely by RET inhibition or how much of a role VEGFR-2 has in its efficacy. Vandetanib seems to have limited EGFR activity [51].

Cabozantinib is an oral multikinase inhibitor with activity against *MET*, *VEGFR2*, and *RET* and is FDA approved for the treatment of metastatic MTC [52]. The recommended dose is 140 mg once daily. It has a terminal half-life of 91.3 ± 33.3 h. It has activity in patients who have progressed on other therapies, including other TKIs, such as vandetanib [53, 54]. The phase III EXAM trial tested 330 patients with radiographic progression of metastatic MTC (219 to cabozantinib, 111 to placebo) and found a median PFS of 11.2 months (cabozantinib) versus 4.0 months in the placebo group (HR 0.28, CI 0.19–0.4). The RR was 28 % cabozantinib and 0 % placebo and no subgroup differences were noted with age, prior TKI treatment, or RET mutational status—hereditary or sporadic. The most common toxicities were diarrhea, HFS, decreased weight and appetite, nausea, and fatigue with dose reductions in 79 % and discontinuation in 16 % of participants [55]. Vandetanib [56] carries a warning for QTc prolongation that is not seen with cabozantinib.

It is notable that the cabozantinib trial placebo group had a PFS of 4 months and the vandetanib trial placebo group had a PFS of 11 months. This difference reflects that the cabozantinib (EXAM) trial only enrolled patients with evidence of progression, whereas the vandetanib trial was not as strict. Additionally, the cabozantinib (EXAM) trial allowed entry of patients who had progressed on one systemic therapy or TKI, whereas the vandetanib trial did not. Although both agents are approved for the first-line setting of metastatic MTC, one could incorporate an off-label use of vandetanib first followed by cabozantinib if or

Table 17.2 Phase III tyrosine kinase inhibitor trials in thyroid cancers

Author and year	Drug dose/trial design	Thyroid CA type	Responses	Safety	Observations
Wells 2012 [51]	Vandetanib 300 mg daily/double-blind, phase III trial	Advanced MTC $n=331$ (231 to vandetanib, 100 to placebo)	– Data cut-off at median follow-up of 24 months – Met primary objective of PFS prolongation HR 0.46, CI 0.31–0.69, $p<0.001$, disease control $p=0.001$, biochemical response $p<0.001$	Diarrhea, rash, nausea, HTN, headache *QTc prolongation	Demonstrated therapeutic efficacy
Elisei 2013 [55]	Cabozantinib 140 mg daily/double-blind, phase III EXAM trial	Radiographic progression of metastatic MTC $n=330$ (219 to cabozantinib, 111 to placebo)	– mPFS was 11.2 months (cabozantinib) versus 4.0 months placebo (HR 0.28, CI 0.19–0.4) – RR 28 % cabozantinib and 0 % placebo. No difference RR (age, prior TKI treatment or RET mutational status—hereditary or sporadic)	Diarrhea, HFS, decreased weight and appetite, nausea, fatigue. Dose reductions in 79 % and discontinuation in 16 %	Responses regardless of subgroup
Brose 2013 [57]	Sorafenib 400 mg bid/ double-blind, multicenter phase III DECISION trial	Locally advanced/ metastatic RAI-R DTC progressed in preceding 14 months $n=417$ (207 to sorafenib, 210 placebo) 57 % PTC, 25 % FTC, 10 %PD	– Met primary end point with mPFS 10.8 months (sorafenib) versus 5.8 months (placebo) HR 0.58, mOS not reached, 70 % of placebo patients started open-label sorafenib – PR 12.2 % versus 0.5 % ($p=0.001$) and SD >6 months 42 versus 33 %	Most common any grade included HFS, diarrhea, alopecia, rash/ desquamation, fatigue, weight loss, HTN	One death in each arm was attributed to study drug
Schlumberger (abstract) 2014	Lenvatinib 24 mg/ day, 28-day cycle/ double -blind, phase III trial. SELECT trial	Progressive RAI-R, previous TKI ≤1 $n=392$	– mPFS 18.3 months (LEN) versus 3.9 months placebo with HR 0.21 [CI] 0.14–0.31; $p<0.0001$; – CR was 1.5 % (4) versus 0 placebo – PRs 63.2 % (165) versus 1.5 % (2) placebo	Treatment-related adverse events were HTN (68 %), diarrhea (59 %), decreased appetite (50 %), weight loss (46 %), nausea (41 %) Over grade ≥3 AEs were HTN (42 %), proteinuria (10 %), weight loss (10 %), diarrhea (8 %), decreased appetite (5 %)	The dose was reduced in 78.5 % of pts and discontinued due to AEs in 14.2 % of pts

AE adverse event, *CI* confidence interval, *CR* complete response, *DTC* differentiated thyroid cancer, *FTC* follicular thyroid cancer, *HFS* hand/foot syndrome, *HTN* hypertension, *HR* hazard ratio, *mOS* median overall survival, *mPFS* median progression-free survival, *MTC* medullary thyroid cancer, *PFS* progression-free survival, *PTC* papillary thyroid cancer, *PR* partial response, *RAI-R DTC* radioiodine ablation refractory DTC, *RET* rearranged during transfection proto-oncogene, *RR* response rate, *SD* stable disease, *TKI* tyrosine kinase inhibitor

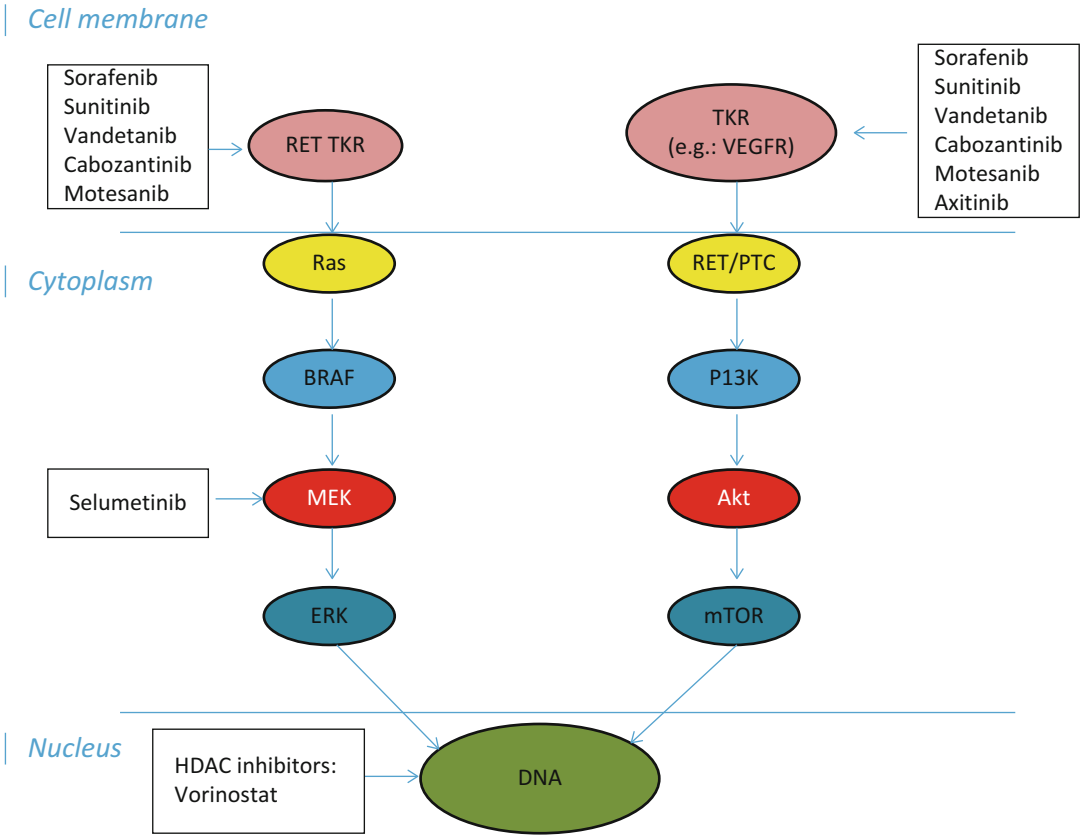

Fig. 17.1 Molecular pathways of medullary and papillary thyroid cancers and their corresponding agents: This is a simplified graphic depiction of the various receptor and intracytoplasmic tyrosine kinases and their corresponding pathways. Intracellular signaling leads to intranuclear modifications at the genetic and epigenetic levels. The two main pathways depicted are the PI3-kinase/Akt/mTOR pathway on the right and the Ras/Raf/MEK/ERK and RET kinase pathway on the left. Sites of targeted pharmacologic activity and their corresponding agents are indicated

when progression occurs since only cabozantinib was tested in that setting. In the opinion of the authors, we would consider vandetanib as the first-line agent followed by cabozantinib in patients with locally advanced or metastatic MTC. Given the more strict criterion (i.e., EXAM trial entry criteria) under which cabozantinib was studied, it makes sense to reserve its use for the second line to ensure a response.

Sorafenib (BAY 43-9006) was FDA approved for the treatment of metastatic DTC in November 2013. It is unique among clinically used tyrosine kinase inhibitors because it was the first compound capable of inhibiting all RAF kinases [1]. It is a small molecule that specifically inhibits Raf kinase, which is a downstream effector that follows from Ras activation. Three isoforms of Raf have been identified, A-Raf, B-Raf, and C-Raf. Additionally, it targets a panel of angiogenic tyrosine kinase receptors such as VEGFR1-3, PDGFRβ, and RET receptors. Thusly, this agent has proapoptotic, via RAF inhibition, and antiangiogenic properties via VEGFR activity. These properties are of special interest to thyroid cancer, which generally displays diffuse neovascularization and variable activating mutations in the MAPK or PI3KCA pathways as mentioned under the "mutational analysis" section. Several phase II trials revealed tumor response to sorafenib (Table 17.2). The phase III DECISION trial presented at ASCO 2013 met the primary end point with a 10.8- versus 5-month mPFS (HR 0.58) in patients with locally advanced and metastatic RAI-R DTC

who had progressed in the preceding 14 months. The OS was not reached. Sorafenib showed an advantage over placebo with a PR of 12.2 % versus 0.5 % and SD of 42 % versus 33 % ($p=0.001$) [57]. This demonstrated a significant advantage over placebo with limited toxicity. Sorafenib is now being studied in combination studies to test efficacy and tolerability.

Lenvatinib is an oral multiple RTK inhibitor targeting VEGFR1-3, FGFR1-4, RET, c-Kit, and PDGFRβ and offers particular potency with regard to inhibition of FGFR-1 which is a well-known mechanism of resistance to VEGF/VEGFR inhibitors [58, 59]. Lenvatinib has shown activity as a monotherapy and in combination with cytotoxic agents for multiple types of solid tumors (ref). There are phase III trials testing its efficacy in various other malignancies [59]. The SELECT trial was multicenter randomized placebo-controlled phase III study of lenvatinib 24 mg/day in a 28-day cycle in 392 patients with progressive RAI-R who were allowed to have received previous TKI therapy. The study found a mPFS of 18.3 months in experimental arm lenvatinib versus 3.9 months in control arm with HR 0.21 [CI] 0.14–0.31; $p<0.0001$; CR rates were 1.5 % for lenvatinib (4 patients) versus 0 for placebo; PR rate was 63.2 % for lenvatinib (165 patients) versus 1.5 % for placebo. The five most common treatment-related adverse events were hypertension (68 %), diarrhea (59 %), decreased appetite (50 %), weight loss (46 %), and nausea (41 %). Grade 3 or higher adverse events (in ≥5 %) were hypertension (42 %), proteinuria (10 %), weight loss (10 %), diarrhea (8 %), and decreased appetite (5 %). The dose was reduced in 78.5 % of patients and discontinued due to adverse events in 14.2 % of patients [60].

There were important differences between the SELECT trial and the DECISION trials (i.e., with sorafenib). Although they tested the same population, the SELECT trial allowed one previous treatment with VEGFR inhibitor and also had a centralized confirmation of progressive disease prior to inclusion (as opposed to being assessed by the investigators in the DECISION trial). These important differences may make it difficult to compare data directly [59, 60].

Table 17.3 highlights selected phase II trials in both DTC and MTC. Representative trials were chosen to bring out unique aspects of experimental therapies as well as highlight select trials that led to phase III trials (in Table 17.2) [61]. For example, a single-arm trial of lenvatinib revealed an impressive 50 % ORR (all PR, 0 CR) with relatively similar effects in setting of previous VEGFR inhibition (41 % RR) versus no prior VEGFR inhibition (54 % RR) which led to the phase III trial in RAI-R DTC. Similarly, the Kloos et al. [2009] study showed a selective activity of sorafenib in PTC over FTC or ATC with a 15 % PR, 56 % SD in PTC, but no response in FTC or ATC and an overall mPFS of 15 months for the entire group [61]. This is one of the phase II sorafenib studies that led to the DECISION trial and its FDA approval for use in locally advanced and metastatic thyroid cancer. Interestingly, the Lam et al. [2010] study shows that sorafenib is also effective in the treatment of MTC, at least in its ability to induce SD (low PR rate 6.3 %) [62]. This is surprising in MTC since sorafenib does not have RET inhibition but blocks down stream Raf signals. The mPFS of the sorafenib arm is similar to other sorafenib studies. Of course, this would need to be verified in a phase III setting. Leboulleux [2012] tested vandetanib in the setting of 145 RAI-R progressive DTC patients in a phase II/III trial and found a PR of 8.3 % versus 5.5 % and SD of 56.9 % versus 42.5 % in vandetanib versus the control groups, respectively [63]. The study demonstrated a median PFS of 11.1 versus 5.9 months in the control group. This study was criticized for the high rate of SD in the placebo group and therefore should be interpreted with caution.

Many other targeted agents are undergoing evaluation on clinical trials. To date, the most successful agents appear to be multityrosine kinase inhibitors (see above FDA-approved agents). Additional TKIs such as sunitinib, lenvatinib, axitinib, VEGF-inhibiting agents, and mTOR inhibitors have shown activity in the phase II setting [64–68]. Many other agents have been tried with more limited success including agents such as vorinostat, celecoxib, rosiglitazone, VEGF trap, thalidomide, selumetinib

Table 17.3 Select phase II trials in RAI-R DTC and medullary thyroid cancer

Author and year	Thyroid CA type	Drug dose/trial design	Responses	Safety	Observations
Lam 2010 [62]	MTC $n=16$	Sorafenib/phase II	6.3 % PR, 87.5 % SD	HFS, diarrhea, HTN	Tumor markers decreased in majority of patients
Kloos 2009 [61]	PTC $n=41$, FTC $n=11$, ATC $n=4$	Sorafenib/phase II	15 % PR, 56 % SD, no response in FTC or ATC, mPFS 15 months	HFS, HTN	Thyroglobulin decreased in 25 %
Sherman (abstract) 2012	RAI-R Progressive DTC, $n=37$	Sorafenib 200 mg bid + temsirolimus 25 mg IV weekly/phase II	No CR but 22 % PR (including 8 % ATC) 38 % PR if no previous chemo, SD 57 %, PD 3 %	SAE: 1 sudden death, colonic perforation	Other combination trials mTOR inhibitors
Leboulleux 2012 [63]	RAI-R Progressive DTC, $n=145$ (72 to vandetanib, 73 to placebo)	Vandetanib 300 mg daily/ phase II/III	8.3 % versus 5.5 % PR; 56.9 % versus 42.5 % SD, $p=0.017$, mPFS 11.1 versus 5.9 months	G3 QTc 14 %, diarrhea 10 %, fatigue 7 %, 2 deaths from SAE (hemorrhage, PNA)	*Note high rate of SD in placebo group
Carr 2010 [69]	Progressive RAI-R DTC $n=28$, MTC $n=7$	Sunitinib 37.5 mg daily/ phase II	3 % CR, 29 % PR, 46 % SD	Leukopenia 34 %, HFS 17 %, diarrhea 16 %, fatigue 11 %	Potential activity in both DTC and MTC *Substantial toxicity
Cohen 2008 [65]	RAI-R DTC $n=45$, MTC $n=11$, ATC $n=2$, 2 other	Axitinib 5 mg bid/phase II	18–30 % ORR, 27–38 % SD (all subtypes)	13 % d/c G3 HTN 12 %, well tolerated	–
Bible 2010 [70]	RAI-R dedifferentiated TC $n=37$	Pazopanib 800 mg daily/ single arm, multicenter	46 %PR, mPFS 11.7 months	43 % ↓dose, skin, fatigue	Many dose reductions
Sherman 2008 [110]	DTC $n=93$	125 mg daily/single arm, multicenter	14 % PR, 67 % SD, mPFS 10 months	25 % HTN, 13 % diarrhea, 5 % abdominal pain, 5 % weight loss, 4 % fatigue	–
Sherman 2011	DTC $n=58$ Lenvatinib (E7080)	Lenvatinib (E7080) 24 mg daily	50 % ORR (0 % CR, 50% PR, 41% RR) (prior VEGFR), 54 % RR (no prior VEGFR)	Grade 3 proteinuria 7 %, fatigue 7 %, diarrhea 5 %	–

ATC anaplastic thyroid carcinoma, *CR* complete response, *DTC* differentiated thyroid cancer, *FTC* follicular thyroid cancer, *HFS* hand/foot syndrome, *HTN* hypertension, *mOS* median overall survival, *mPFS* median progression-free survival, *mTOR* mammalian target of rapamycin, *MTC* medullary thyroid cancer, *ORR* overall response rate, *PFS* progression-free survival, *PNA* pneumonia, *PTC* papillary thyroid cancer, *PR* partial response, *QTc* QT (intervals, c=corrected), *RAI-R DTC* radioiodine ablation refractory DTC, *RET* rearranged during transfection proto-oncogene, *RR* response rate, *SAE* serious adverse event, *SD* stable disease, *TKI* tyrosine kinase inhibitor, *VEGFR* vascular endothelial growth factor receptors

(AZD6244), romidepsin, and vemurafenib (BRAF inhibitor) [64]. Carr et al. [2010] showed that sunitinib had overall responses similar to sorafenib but with a greater toxicity profile [69]. Cohen et al. in a study with DTC highlighted the activity of axitinib, a tyrosine kinase inhibitor approved for RCC in 2012, in a variety of thyroid cancers but had modest ORR of 18–30 % [65]. Bible et al. (2010) showed that pazopanib induced a high rate of PR (46 %) with comparable mPFS to sorafenib but had many dose reductions (43 %) [70]. Motesanib is an angiokinase inhibitor that antagonizes VEGF receptors and had levels of activity in DTC [71] comparable with sorafenib along with a similar sorafenib-like side effect profile; see Table 17.3. Of these multityrosine kinase inhibitors, only sorafenib and lenvatinib have gone on to phase III trials.

Combination studies are of interest as multiple targeted blockades and hold promise for greater efficacy and future directions. Sherman [72] et al. (2012) is an example of a combination study where daily oral sorafenib 200 mg bid and IV temsirolimus 25 mg weekly effectively induced a slight increase in PR 22 % (i.e., PR 8 % in ATC, and 38 % in the setting of no previous chemotherapy; SD of 57 % and only 3 % progressive disease) over other sorafenib monotherapy studies (e.g., DECISION [57] trial with a PR 12.5 %). However, this combination study incurred a sudden death on the trial due to colonic perforation. Although combination studies of a TKI and mTOR show similar or even enhanced efficacy [64, 73] to TKI monotherapy, the adverse side effects remain in question and challenge the adaptation of combination trials.

Upon review of phase II and phase III data, it is clear that these targeted modalities have activity but do not induce durable responses. Benefits of TKIs may be inexistent or transient due to distinct mechanisms of drug resistance that leads to tumor progression. Two distinct mechanisms of resistance have been described for the VEGF pathway inhibitors [74]. Intrinsic resistance is conferred via the tumor microenvironment and numerous mechanisms to restore growth such as upregulation of alternative proangiogenic signals leading to revascularization among others [59]. Therefore, many patients either stop responding or discontinue due to toxicity with increasing dosage of drug. Salvage therapy or combination therapy with lower toxicity profiles will become increasingly important. A recent retrospective single institution review showed that patients who received salvage therapy with agents such as sunitinib, pazopanib, cabozantinib, lenvatinib, and vemurafenib in the metastatic setting had a statistically significant longer OS (58 vs. 28 months $p=0.013$) compared with patients who only received first-line sorafenib [75]. Although the patient groups were matched, the retrospective nature of this study may induce bias. Regardless of a potential bias induced by the retrospective nature of this study, the next step is to prescribe serial targeted therapy according to duration and side effect profile in a consecutive manner.

Another approach to targeting RAI-DTC is to redifferentiate the cancerous thyroid cell that has lost its iodine avidity to restore its iodine uptake function. This data has not progressed as far as what is known about activating mutational status although the principle is clearly very similar and loss of iodine avidity is related to mutational complexes (i.e., BRAF mutation loss of iodine avidity). Preclinical data show that BRAF-mutated thyroid cancer cells treated with MEK inhibitors are able to reestablish NIS expression and ^{124}I uptake. The MEK inhibitor selumetinib has been pilot tested in 20 patients with RAI metastatic DTC [26] (Ho 2012) where the RAI avidity of thyroid tumors was quantified by lesional dosimetry with ^{124}I PET imaging in patients, before and after 4 weeks of treatment with selumetinib. For patients whose tumors reacquired the ability to take up RAI, ^{131}I treatment was administered, and tumor response was assessed both radiographically and with measurement of the serum tumor marker thyroglobulin (Tg). Of the 20 patients, nine patients had tumors with the BRAFV600E mutation, five patients had tumors with NRAS mutations, three patients had tumors with RET/PTC rearrangements, and the remaining three patients were wild type for these alterations. Twelve of the 20 patients in the study demonstrated increased tumoral ^{124}I uptake, and

8 of these 12 patients achieved sufficient iodine reuptake to warrant treatment with ^{131}I. Interestingly, five of these patients were found to have NRAS mutations, one a BRAF mutation, one a RET/PTC rearrangement and one patient was wild type. Further genotyping and cytogenetic analysis is ongoing to discover other potential oncogenic drivers that may have promoted susceptibility to this therapeutic strategy. The increased iodine incorporation as quantified on the ^{124}I scans translated to clinical efficacy with RAI therapy. Reduction in tumor size by RECIST criteria was achieved in all RAI-treated patients, with five confirmed partial responses and three patients with stable disease. Substantial decreases in serum thyroglobulin following RAI therapy were achieved in all eight RAI-treated patients. The mean percent reduction in serum thyroglobulin achieved "post-RAI" (2 months after RAI treatment) compared to "pre-RAI" (within 3 weeks before RAI treatment) was 89 %. Data from the pilot study also suggests that pretreatment with selumetinib selectively increased RAI uptake in tumoral lesions compared to nonthyroidal tissue (salivary gland).

This pilot study by Ho et al. demonstrates that MAPK pathway inhibition can modulate RAI uptake in the most difficult clinical scenario: patients with resistance to RAI therapy. Most patients in the pilot clinical study described above had many metastatic lesions, some of which were refractory to RAI at baseline, and some of which were partially RAI avid at baseline. Selumetinib not only restored RAI uptake in previously refractory lesions but also increased RAI uptake in most partially avid lesions (typically by more than 100 % compared to the baseline value; three- to sevenfold increases in maximum SUVs were observed). In addition to the Ho et al. pilot study described above, a phase II study of 100 mg bid selumetinib in 39 patients with RAI-refractory differentiated metastatic thyroid cancer involved continuous monotherapy dosing of selumetinib and no RAI treatment [76]. The results demonstrated few clinical responses (one partial response in 32 evaluable patients) but demonstrated a 66 % stable disease rate; median PFS in this poor-prognosis cohort was 33 weeks in patients with mutations in BRAFV600E and 32 weeks in all comers. Although this study was conducted with the mix and drink formulation (from which selumetinib exposure may be lower), the efficacy of selumetinib as monotherapy in this population was disappointing [76].

Other forms of new targeted therapies include the experimental use of immunotherapy in thyroid cancer. Preclinical studies have shown the promise of both CTLA-4 and PD-1 targeting to release negative immunological feedback mechanisms that certainly may play a role in maintaining a more indolent disease [77–79].

Future Directions of Targeted Therapies

Thyroid cancer is on the brink of "personalization" as mutations will soon confer higher risk and prognostic categories. Yet, true "personalization" may be a ways off given the lack of current ability to assign treatments based on mutational status. Targeted therapies are likely to play an increasingly important role in the adjuvant, neoadjuvant, and combination settings for the treatment of thyroid cancers. The future of targeted therapies in thyroid cancer will focus on agents that produce greater efficacy, less toxicity, potential combinations, and understanding resistance mechanisms. Clinical practice will continue to dictate where the evidence is lacking and the unexplored areas of thyroid cancer management. Greater experience with the agents that are currently available will guide the intelligent use of these agents to their fullest potential and will likely include expanded use indications. A better understanding of exactly how these agents work is needed to more effectively design treatment paradigms. For example, these new agents raise the question of whether there is any potential benefit to their concurrent use with cytotoxic chemotherapy or whether they can be used in a consolidative or maintenance fashion. The questions and answers will continue to evolve as a deeper appreciation for the driver mutations is eluci-

dated and novel targeted therapies continue to advance such that many of the questions we ask today may not be entirely relevant in 10 years.

Certainly, there is a temptation to expand the use of these agents in off-label settings as clinical data in certain specific scenarios or treatment dilemmas are lacking. A clinician may hope to induce a rapid CR for symptom relief or make the patient a candidate for surgery. In other cases, ensuring SD may be the goal. In general, there is less familiarity with the use of TKIs in the up-front, adjuvant, or after previous TKI failure settings. Therefore, it is reasonable to postulate some nonconventional uses for these drugs, perhaps even with the use of experimental cytotoxic agents. The following cases will illustrate these types of potential questions. They are controversial because there is no current standard of care to refer to since these drugs are emerging. The discussion that follows will attempt to answer these controversial questions and provide some references.

Controversial Questions

1. What is the role of neoadjuvant use of TKI in locally thyroid cancers?
2. What is the role of neoadjuvant use of TKI in metastatic DTC? (Can surgery be replaced or what is the role of TKIs or chemotherapy as an organ-sparing approach?)
3. Role in adjuvant setting?
4. Role of TKI in definitive setting (e.g., RT + TKI)

Case #1

A 56-year-old male has an enlarging 11 cm neck mass that is confirmed to be papillary thyroid carcinoma including an admixture of the rare thyroid squamous cell carcinoma. A surgeon determines that a standard operation would cause a significant increase in likelihood of morbidity. Given the more aggressive variant, he wants to achieve an R0 resection.

Is there a role for the neoadjuvant use of tyrosine kinase inhibitors or chemotherapy prior to thyroidectomy in locally advanced, "nonmetastatic" DTC?

Neoadjuvant therapy would potentially make this surgery easier and could provide information about how responsive the cancer is to these newly approved therapies (e.g., as is frequently done in triple negative breast cancer neoadjuvant therapy). However, standard guidelines (e.g., NCCN) do not recommend either therapy in the neoadjuvant setting given the lack of uniform evidence. There is no currently identified role for the use of targeted therapies in the up-front or neoadjuvant setting. Although there is limited evidence to guide these particularly aggressive situations (e.g., aggressive mixed squamous cell histology and size), opportunities to offer more aggressive individualized therapy should certainly not be overlooked.

The neoadjuvant use of standard cytotoxic chemotherapies has been described and tested and provides greater evidence for the response for neoadjuvant treatment than targeted therapies at this point. In a case series presented by Ito [2012], three patients with papillary thyroid carcinoma and a squamous cell carcinoma component, just as in this case, were treated neoadjuvantly with weekly paclitaxel as an induction therapy. The partial response rate was 67 %, and the clinical benefit rate (i.e., PR and SD) was 100 % such that two out of the three cases went on to receive a definitive operation [80]. Additionally, a retrospective review of 16 patients from 1988 to 2005 with very locally advanced papillary thyroid carcinoma (PTC) showed a decrement in tumor size of over 50 % in 44 % of patients at the time of surgery [35]. The rest of the patients showed a decrease in tumor size of less than 50 % using vinblastine in 11 cases, vinblastine with Adriamycin in two cases, and other chemotherapy schedules in the remaining three cases. The mean tumor diameter was 9.67 cm and seven patients had a pT4 tumor. These tumors were likely inoperable prior to neoadjuvant therapies. Regional and distant metastases were detected in ten and seven patients, respectively.

Evidence for the use of neoadjuvant induction chemoradiation may be extrapolated from a review by Tennvall (1994) of anaplastic thyroid carcinoma (ATC) for its use in perhaps more aggressive or borderline operable cases. The

review consisted of 33 patients who were treated with hyperfractionated radiotherapy, doxorubicin 20 mg/m^2 per week, and found that 70 % were able to receive debulking surgery and no patient failed to complete the protocol due to toxicity [81]. In this almost universally fatal disease, this intervention successfully decreased the rate of local failure to only 48 % where the cause of death was attributed to local failure in only 24 % thus preventing death from suffocation or large local tumor ulceration. Although unable to ultimately stop progression of the disease, the combination of RT and doxorubicin did work to reduce local failure rates in the ATC population.

Chemotherapy combinations produce excess toxicity but also have been shown to induce greater complete or partial responses and should not be overlooked in a curative or neoadjuvant setting. For example, although the Shimaoka (1985) study [31] did not show a significant overall difference between single-agent doxorubicin versus doxorubicin and cisplatin, there was a trend towards significance (17 % vs. 26 %) and the combination group contained five patients who obtained a CR where the single-agent group contained not a single CR. Additionally, the single case by Crouzeix (2012) reported on the ability to obtain a CR twice with combination of chemotherapy in a patient who had progressed on multiple lines of targeted therapy [82].

Both chemotherapy and the recently approved TKIs, sorafenib in RAI-R DTC and vandetanib and cabozantinib in progressive medullary thyroid cancer, were approved based on their benefit in the metastatic or locally advanced/inoperable cases. Although chemotherapy is the only medical modality that has minimal data in the neoadjuvant setting thus far, there is no reason to think that the biology of untreated locally advanced thyroid cancer is necessarily different from untreated metastatic thyroid cancer. If this patient had confirmed well-differentiated thyroid cancer (follicular, papillary, Hürthle cell, etc.), for example, sorafenib could be given in an off-label neoadjuvant fashion. However, there would be no treatment guidelines for end point or treatment duration. Also, these targeted therapies provide a complete or partial response that could potentially lead to operability in only a minority of patients. And there is the possibility that by introducing these agents earlier while there is considerable tumor burden, this could select for more formidable clones and thus decrease later treatment responses further into this patients treatment course (or if, e.g., he recurs).

In summary, a patient with a large and/or inoperable tumor could benefit from downstaging with neoadjuvant chemotherapy as per Besic (2013) [35], Ito (2012) [80], or Tennvall (1994) [81]. Although more conclusive definitive studies using neoadjuvant therapies are scarce and have not been done to assess for long-term consequences, it could be considered if the goal is to obtain operability that would ultimately provide for a better and more sustained outcome.

Case 2

A 65-year old female presents with oligometastatic differentiated thyroid cancer and larynx invasion. A biopsy confirms a BRAF mutation. A PET scan reveals FDG avidity in both the thyroid and larynx abutting the trachea but not in any other area of the body. Radioiodine imaging is not possible at this time due to recent contrast use during CT imaging that limits a metastatic workup of non-FDG avid lesions. Both the surgeon and the radiation oncologist want to discuss if there is any role for treating with curative intent in this oligometastatic patient and if there is any role for a tyrosine kinase inhibitor or chemotherapy to treat this patient in with neoadjuvant intent or should treatment (e.g., radiation) be only given with less aggressive, palliative intent.

*Is there a role for the use of a neoadjuvant TKI in locally metastatic DTC in order to provide an organ-sparing approach? (*i.e., *can surgery be replaced?)*

Once thyroid carcinoma has transgressed the glandular capsule with invasion into either the larynx or the trachea, there is a distinct reduction in local control and survival after surgery. Even in the case of a well-differentiated DTC after surgery, the 10-year rate of local failure is 28.1 % and deemed unacceptable [83]. This case is asking whether there is evidence to give sorafenib or perhaps a BRAF inhibitor or another targeted agent or chemotherapy in the up-front oligomet-

astatic setting so that the patient may benefit from an organ-sparing approach instead of undergoing an operation that will sacrifice the larynx and fail upwards of one-third of the time at 10 years.

The management of laryngeal or tracheal invasion is primarily surgical with several options such as tangential excision of tumor, tracheal or laryngeal sleeve resection, total laryngectomy, and cervical exenteration or palliative resection [84]. Nonsurgical options typically include RAI for which there is very limited data, but it is routinely performed and has limited effectiveness if there is substantial tumor bulk (i.e., would be more effective to treat microscopic disease) or EBRT; however, this is only used in the adjuvant or palliative setting as this maneuver increases the risk of airway obstruction and complications [84]. It is unlikely for radioiodine ablation to be dramatically effective if there is a large lesion invading the larynx with a large concomitant thyroid lesion, but it could be effective for smaller pulmonary subcentimeter lesions, for example.

A TKI, such as sorafenib or lenvatinib, could be used off-label; however, an operation should never be delayed given that response rates are variable and the goal here would be to achieve a cure and just stable disease. In cases that are on the border of operability, quality of life may be maintained (i.e., no laryngectomy) by considering definitive induction targeted or chemotherapy plus EBRT similar to head and neck SCC that are on the border of resectability. A potential option for this patient would be vemurafenib as this drug is currently undergoing trials in thyroid cancers specifically with BRAF mutations and has been shown to reduce pulmonary lesions by 31 % and has a duration of response of 7.6 months in patients with BRAF-mutated metastatic PTC in a phase I setting [85]. Phase II trials with vemurafenib are not currently available. Additional multikinase targets are starting to be studied as a form of salvage treatment [75]. With salvage therapy, partial responses were seen in 7 of 17 (41 %) and stable disease in 10 of 17 (59 %) patients. Median progression-free survival was 7.4 months with first-line sorafenib and 11.4 months with salvage therapy. Salvage therapy included sunitinib ($n=4$), pazopanib ($n=3$), cabozantinib ($n=4$), lenvatinib ($n=3$), and vemurafenib ($n=3$) [75]. Another potential option would be a head and neck squamous cell carcinoma regimen such as concurrent cetuximab and EBRT, but that has not been studied in the setting of thyroid cancer with tracheal invasion and could not be recommended at this time without any evidence of support.

Additionally, one could consider an unconventional maneuver to increase susceptibility to cytotoxic chemotherapy that is a pretreatment of TSH stimulation prior to giving chemotherapy. A series of 14 patients with poorly differentiated thyroid carcinoma and nonfunctioning diffuse lung metastasis were enrolled to receive carboplatin and epirubicin at 4–6-week intervals after TSH stimulation with a recombinant human TSH agonist or by simply reducing levothyroxine levels [33]. The overall rate of CR and PR was 37 %, and an ORR (including SD) was found in 81 % of patients as well as a greater than 50 % reduction in serum thyroglobulin after chemotherapy. This maneuver resulted in halting the progression of disease in 6 of the 14 patients with lung parenchymal disease. It would be possible to use this maneuver to definitively treat with curative intent cases of locally oligometastatic disease with borderline operability. Although doxorubicin is not known to be a radiosensitizing chemotherapy, the study by Kim [86] [1983] showed high rates of local control when used concomitantly. Tyrosine kinase inhibitors are also not known to be radiosensitizing in the same way that some specific inhibitors have shown radiosensitizing activity in the preclinical setting (e.g., aurora kinase inhibitors).

In summary, there is very limited evidence for the use of any combination of targeted therapies, chemoradiation, and radiosensitizing agents to definitively treat locally metastatic disease with organ-sparing nonsurgical curative intent. One may consider TSH stimulation to induce a greater chemotherapy response per Santini (2002) or the concomitant use of EBRT with doxorubicin either to induce a neoadjuvant response to encourage an organ-sparing approach or as definitive treatment in borderline cases where organ sparing is not an option.

Case 3

A 32-year-old female with a history of a pheochromocytoma and mucosal neuromas has a rapidly enlarging neck mass. Pathology reveals well-differentiated MTC and staging shows localized disease. Molecular testing reveals a RET translocation. The patient is diagnosed with a multiple endocrine neoplasm type 2A. A total thyroidectomy is planned, and the surgeon wants to know if there is any role for the newly approved vandetanib or cabozantinib in the adjuvant setting.

Is there a role for TKI therapy in the adjuvant, postsurgical setting?

Medullary thyroid cancer (MTC) is a progressive but indolent form of neuroendocrine tumor and represents a more aggressive form of thyroid cancer. There is a tendency to spread quickly to locoregional lymph nodes at presentation that makes early definitive surgery difficult. A total thyroidectomy and lymphadenectomy will result in biochemical remission and cure in 40 % of cases [25]. MTC is derived from the C cells of the thyroid follicle, which represents a variant of a neuroendocrine cell that produces calcitonin and does not concentrate iodine. Therefore, standard radioiodine ablation is not nearly as effective as in DTC but is still toxic to the cell and achieves minimal cytotoxicity via a bystander effect.

At present, both vandetanib and cabozantinib are FDA approved in the metastatic setting of medullary thyroid carcinoma and have not been brought to the up-front or adjuvant setting nor have the other tyrosine kinase inhibitors for other types of thyroid cancer, at this point. In fact, vandetanib and cabozantinib are only recommended if metastatic lesions are larger than 1–2 cm in diameter and grow faster than 20 % per year or for patients with symptoms related to multiple metastatic foci that cannot participate in a clinical trial. Cytotoxic chemotherapy with dacarbazine-based regimens such as cyclophosphamide/vincristine/dacarbazine is an alternate option for those patients who cannot tolerate or fail multiple TKIs and would combine dacarbazine with other agents, including vincristine, 5-fluorouracil, cyclophosphamide, streptozocin, or doxorubicin. However, no significant advantage is seen with one regimen over another; all of the regimens only achieve a 10–20% partial response and, most importantly, are only given in the metastatic setting.

Vandetanib and cabozantinib may provide useful off-label adjuvant therapies for particularly aggressive cases of MTC where surgical margins are positive and/or lymphovascular invasion is present, for example. These targeted agents would be advantageous in a particularly aggressive case with the aforementioned characteristics that prognosticate limited up-front control of the disease. Additional treatment modalities, specifically for MTC, have not been brought to the adjuvant setting. Somatostatin inhibitors have not been found to be useful as a single agent [87, 88] or in combination with interferon-α2b [89]. In general, somatostatin inhibitors such as octreotide have limited efficacy in MTC [90, 91]. However, testing of the long-acting pegylated version of octreotide combination with chemotherapy has yet to produce results [92].

Adjuvant therapy enhancement for RAI-R DTC, but not for MTC, may be possible if iodine receptor mechanism of the tumor could be reestablished thus enhancing the effectiveness of radioactive iodine treatments that are routinely given in the adjuvant setting to get rid of residual thyroid or thyroid cancer cells throughout the body. The first redifferentiation agent was isotretinoin (a version of retinoic acid) that was able to produce redifferentiation in 38 % of cases. A second attempt at redifferentiation was made with PPAR-gamma (peroxisome proliferator-activated receptor gamma) rosiglitazone that has since been taken off of the US market. Results with posiglitazone (another PPAR) have not been as promising. The next case will discuss current redifferentiation strategies further.

Case 4

A 70-year-old adopted healthy male is diagnosed with a well-differentiated papillary thyroid cancer found on thyroid and sternal biopsies. The ultrasound of the thyroid revealed associated regional lymphadenopathy. Radioiodine and PET scans reveal no other sites of distant metastasis.

He is to undergo a total thyroidectomy with subsequent radioiodine ablation to destroy any residual thyroid tissue and EBRT to the sternal lesion. The surgeon wonders if there might be a role for sorafenib to be started as an adjuvant treatment along with RAI.

*What is the role of TKIs in the oligometastatic setting with a regional site of metastasis in an attempt to treat the patient definitively with curative intent (*e.g., *role of TKI to ensure remission—can it be used in addition to RT + chemotherapy or as a consolidation/maintenance treatment)?*

Frequently, thyroid cancer presents at a more advanced stage or even with low-grade metastasis (lower tumor bulk), and it is possible to treat the patient with aggressive therapy, including SBRT, in order to try to obtain a cure. Technically, this patient has stage IV metastatic disease but also has a chance at cure given the low burden of metastatic disease. According to American Thyroid Association recommendations, extracervical metastasis should be treated with EBRT if there is concern for a pathological fracture, neuroskeletal or compartmental compromise, pain, or areas of radioiodine or FDG avidity [93]. In addition, extracervical metastasis can be treated more aggressively than the recommendations when attempting to reduce tumor bulk in an effort to downstage a patient or achieve durable remission or cure.

A potentially common question will arise in this era of TKI therapy: what else can we do to ensure a cure? Are there any data to support giving a TKI in the definitive treatment setting, that is either concurrently with SBRT, adjunctively in morphologically aggressive or locally advanced differentiated thyroid cancers, or as a consolidation treatment, once a remission is obtained?

TKIs are currently approved for use in the metastatic setting and could certainly be considered in this case. Given that the treatment goal is curative, there is a theoretical consideration for the selection of new mutational clones based on clinical data in other settings, but there are also extremely limited data to guide clinical decision making about TKIs with an advanced thyroid cancer in this setting. Recent evidence suggests that the likelihood of achieving remission varies depending on the size of the primary tumor, extent of invasion, or lymph node status as defined by number and size of affected nodes [94, 95]. Thus, one could make an argument for the potential use of a TKI as a maintenance therapy; however, much work would need to be done to classify which types of thyroid cancer would meet requirements for maintenance TKI treatment given the indolent nature of the majority of DTC.

As mentioned previously, thyroid cancer stage depends on histology, as all anaplastic thyroid cancer is automatically stage IV [96]. This is a very rare classification strategy that is not used in other cancers but make sense for thyroid cancer as its behavior can be predicted from its histology, and we are starting to understand its behavior based on mutational driver analysis as well [74].

Thyroid cancer deaths are exceeding rare if remission is achieved, and studies have shown that nearly all deaths ultimately occur in the group of patients who do not achieve remission [94, 96]. Disease-specific death was reported in 6 % and 8 % of patients who did not achieve remission compared to 0 % in patients who achieved remission in two studies where there was a median follow-up time of 7 and 10 years, respectively [94, 95]. Logically, the mortality rate continues to rise with greater period of follow-up time. The majority of patients who achieve remission do not relapse and the rate of relapse has been shown to be 1–4 % when patients are followed for a median of 5–10 years [94, 95]. Thus, even high-risk patients with morphologically/histologically aggressive presentations can demonstrate an excellent prognosis if they are able to achieve an up-front early remission. There is also a considerable psychological benefit for patients who are able to achieve a remission and are then reclassified as low risk and require much less frequent thyroglobulin testing, imaging requirements, and less aggressive TSH-suppressive therapy. Supraphysiological dosing of levothyroxine places the patient at risk for atrial fibrillation, osteoporosis, and psychological consequences of anxiousness and fatigue while in the mildly hyperthyroid state.

Another reason to provide multipronged aggressive therapy initially is that failure to achieve initial remission will result in subjecting the patient to potentially many more lines of additional therapies to control the disease further on in the disease trajectory (e.g., more RAI, surgery, external beam irradiation). Therapeutic RAI is associated with a cumulative dose-related risk of early- and late-onset complications such as salivary gland damage, dental caries, nasolacrimal duct obstruction, and decreased fertility [97]. Furthermore, a dose-dependent relationship is also seen between cumulative administered RAI activity and the subsequent occurrence of secondary malignancies, especially in younger populations [98, 99]. All of these risks and symptoms constitute significant quality of life issues for the patient. The inconvenience of repeating a low-iodine diet, the associated radiation safety precautions, and missed days of work are additional factors the patient must consider. Additional surgery carries associated risks related to anesthesia, nerve damage (resulting in hoarseness, permanent tracheotomy in rare occasions, drooping eyelid, loss of control of shoulder muscles, and loss of sensation in the neck), increased scarring in the neck (resulting in discomfort and difficulty swallowing), and damage to the parathyroid glands (resulting in hypocalcemia and a lifetime need for vitamin D and calcium supplementation and frequent blood tests). Thus, avoidance of further therapy is beneficial to the patient.

Unfortunately, additional therapy is often less effective, particularly in patients with persistent structural disease [100]. Further, RAI can be given to patients that have persistent biochemical evidence of disease, and although repeat RAI is often less effective than the initial RAI treatment (especially for patients with persistent structural disease), it can be effective at driving some patients with persistent biochemical disease into remission [101]. Thus, strategies designed to improve the tumoricidal effect of the initial RAI dose should result in higher remission and cure rates [95].

Diagnostically, it would be helpful to have histological/biochemical/mutational status indicators to guide a clinical judgment in the administration of more aggressive or up-front therapies. For instance, in addition to stage, thyroid-specific BRAFV600E mutations have been shown to confer higher rates of recurrence, but this still has not translated into clinical practice. Experimentally, one could consider the administration of vemurafenib to these patients up front to induce a remission status.

Therapeutically, an intervention that enhances the effectiveness of initial therapeutic RAI in high-risk patients should result in higher remission rates and remove the need for further therapy and would thus be of clear benefit to patients. In the pilot study by Ho (2012) as mentioned previously, most patients had numerous metastatic lesions, some of which were refractory to RAI at baseline and some of which were partially RAI avid at baseline [26]. Importantly, selumetinib pretreatment not only restored RAI uptake in previously refractory lesions but also increased RAI uptake in the majority of partially avid lesions (typically by more than 100 % compared to the baseline value; three- to sevenfold increases in maximum SUVs in such lesions were consistently observed). This pilot data not only supports the preclinical hypothesis that inhibiting the MAPK pathway can convert non-RAI avid lesions to RAI avid tumors but also demonstrates that iodine uptake in previously iodine sensitive lesions can be significantly increased with selumetinib [26]. This observation broadens the potential clinical applicability of this approach beyond just RAI-refractory thyroid cancer, to the use of selumetinib and RAI as part of up-front adjuvant treatment of RAI-naïve and susceptible DTC. Side effects of selumetinib are considered tolerable, predictable, manageable, and reversible (mainly from rash and fatigue). The long-term risk of secondary malignancy from a single dose of 100 mCi dose is extremely rare as this risk accumulates with cumulative dosing.

The same rationale applies for using a TKI (e.g., sorafenib) as consolidative therapy. However, one always has to make a clinical decision for which there may not be evidence-based data. It may behoove the patient to accept additional therapy if there are aggressive locally advanced metastatic features or there is presence

of a mutation that could be selectively treated. Another generally accepted method would be to have the patient take recombinant TSH to stimulate thyroid cancer cells prior to giving definitive treatment (e.g., Santini 2002) [33] as mentioned previously for case 1.

Quality of Life with Targeted Therapies for Thyroid Cancers

Fatigue has been the most disabling symptom of multityrosine kinase inhibitors and is universally reported with all of them [102]. Fatigue was initially reported with imatinib [103] and has since been reported with all TKIs. Cognitive impairment (i.e., memory/concentration impairment) has also been reported, for instance, with sorafenib or sunitinib use in metastatic renal cell carcinoma and gastrointestinal stromal tumors [104]. Worse impairment was associated with longer period of use and concomitant VEGF activity [104]. Diarrhea and hand/foot syndrome are also very common across most TKIs. Hemorrhage and gastrointestinal perforations have been seen with cabozantinib [52]. Prolonged QTc and pseudomembranous coli has been reported with vandetanib [50].

Further quality of life indicators are needed especially as patients are taking targeted therapies for extended periods of time. It has been noted that patients often have misconceived ideas about the meaning of "personalized medicine" [105].

Conclusions

This chapter reviewed nonsurgical treatments of thyroid cancer and focused on the evidence for targeted therapy paradigms and the potential for their utilization alongside conventional cytotoxic chemotherapy in thyroid cancers. Controversial real-life clinical dilemmas were reviewed as a way to inspire clinical creativity in addressing nonsurgical management opportunities for the patient with thyroid cancer. The chapter focused primarily on the most common types of well-differentiated thyroid cancers (e.g., papillary and follicular) and particularly RAI-R DTC. Management of MTC was also addressed albeit more peripherally.

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