Chapter 12
Surgery for Thyroid Nodules

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Introduction

Palpable thyroid nodules are common, with a prevalence of 4–7% in the general population [1]. Subclinical thyroid nodules are even more common and are detected in 19–68% of healthy patients without known thyroid disease [2]. Frequently, thyroid nodules are incidentally identified on imaging studies: 67% of cervical ultrasounds, 16% of computed tomography scans, 9% of carotid duplex studies, and 2–3% of positron emission tomography scans have been reported to include thyroid nodules that were not anticipated based on history and physical examination [3]. The high frequency of incidentally identified thyroid nodules has led to a significant increase in the number of thyroid biopsies and subsequent thyroid surgeries performed in the USA. Indeed, over a 5-year period, there was a 107% increase in the number of fine needle aspiration (FNA) biopsies of the thyroid, such that by 2011, nearly two thirds of all tissue biopsies performed in the USA were on the thyroid. Almost certainly as a result, the number of thyroid nodule-related operations also increased by 31% over the same period. The frequency of total thyroidectomies increased by 12% per year, while lobectomies only increased by 1% per year, such that by 2011, the majority of patients (56%) underwent total thyroidectomy [4].

The incidence of thyroid cancer has increased over the last several decades at a pace faster than any other malignancy in the USA, with 62,450 new cases diagnosed in 2015 [5]. This has almost exclusively been due to an increase in the incidence of papillary thyroid cancer (PTC), as the incidence of other primary thyroid malignancies has remained stable. The increase in incidence of PTC also has been seen in several other high-income countries; most notably, a thyroid cancer screening program in South Korea that was initiated in 1991 ultimately is believed to have led to a 15-fold increase in the incidence of PTC between 1993 and 2011 [6]. This suggests

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that much of the increased incidence in thyroid cancer is due in part to surveillance bias. that is, an increase in (largely radiological) detection of clinically insignificant tumors [7]. However, the number of large thyroid tumors has increased as well [8], suggesting that factors other than improved detection, such as obesity or environmental factors, also may be contributing to the international epidemic of thyroid cancer [9].

Thyroid surgery is the mainstay of treatment for thyroid cancer and nodules suspicious for cancer. Hyperthyroidism and compression from thyroid goiter are the two other indications for thyroid surgery. Treatment guidelines have been created by the American Thyroid Association (ATA) to inform clinicians, patients, researchers, and health policymakers based on published evidence related to the diagnosis and management of hyperthyroidism and other causes of thyrotoxicosis (2016) [10], adult patients with thyroid nodules and differentiated thyroid cancer (2015) [11], children with thyroid nodules and thyroid cancer (2015) [12], medullary thyroid cancer (2015) [13], and thyroid disease during pregnancy and postpartum (2011) [14]. These guidelines inform clinical decision-making for the surgical management of patients with thyroid nodules in different clinical settings and are referenced throughout the following chapter.

Preoperative Evaluation

Patients referred for consideration of thyroid resection for nodular disease should have a thorough history to evaluate for symptoms and signs of hyper- and hypothyroidism and local compression, risk factors for thyroid cancer, and a family history of thyroid cancer and/or other endocrinopathies. Symptoms of hyperthyroidism include weight loss, anxiety, hair loss, palpitations, heat intolerance, and insomnia. Symptoms of hypothyroidism include weight gain, fatigue, cold intolerance, and constipation. Symptoms of local compression include a globus sensation, dysphagia, dyspnea, and dysphonia and may be due to goiters or large nodules that compress surrounding structures and especially the aerodigestive tract. In the setting of malignancy, these symptoms are concerning for locally advanced disease and may be due to invasion into surrounding structures. Dysphonia may be due to tumor invasion into the recurrent laryngeal or vagus nerves. Rapid nodule growth or onset of symptoms is concerning for an aggressive malignancy. Risk factors for thyroid cancer include a history of radiation exposure (particularly in childhood or adolescence), family history of thyroid cancer (such as familial medullary or PTC), and history of a familial cancer syndrome, such as multiple endocrine neoplasia (MEN) Type 2.

Physical examination should focus on the thyroid gland and cervical lymph nodes. Firm or irregular nodules are concerning for malignancy. Enlarged cervical lymph nodes are concerning for metastases. Fixed nodules and/or extensive lymphadenopathy are concerning for locally advanced disease. Inability to palpate the inferior aspect of the thyroid gland or a positive Pemberton's sign should raise

concern for thyroid extension into the mediastinum. The patient also should be evaluated for signs and symptoms of hyperthyroidism, including anxiety, tremor, heat intolerance, tachycardia, palpitations, weight loss, lid lag, exophthalmos, orbital edema, and pretibial edema.

The 2015 ATA Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer [11] recommend that all patients with thyroid nodules have a TSH drawn to evaluate thyroid function. If the TSH is suppressed, a radionuclide thyroid scan should be obtained to determine if the nodule is hyperfunctioning. A radionuclide scan is not recommended for patients with a normal or elevated TSH. Fine needle aspiration of hyperfunctioning thyroid nodules is not recommended, since these nodules are rarely malignant. A calcium level should be obtained to evaluate for hyperparathyroidism in the appropriate setting. If hyperparathyroidism is identified, parathyroidectomy should be performed at the same time as thyroid surgery. Patients with medullary thyroid carcinoma (MTC) or a suspicion of MTC should have serum calcitonin and carcinoembryonic antigen (CEA) tumor markers drawn prior to surgery. These levels correlate with extent of disease and provide important prognostic information. Patients with calcitonin levels >500 pg/mL are at risk for distant metastases and should have a neck/chest computed tomography (CT) scan, liver magnetic resonance imaging (MRI), and bone scan to evaluate for distant metastases [13]. All patients with a new diagnosis of MTC should have genetic counseling and testing performed, since 6–7% will harbor an unsuspected RET proto-oncogene germline mutation and MEN2 syndrome [15]. Patients with an unknown or positive RET mutation should have laboratory testing to exclude pheochromocytoma and primary hyperparathyroidism prior to surgery. If diagnosed with pheochromocytoma, adrenalectomy should be performed prior to thyroidectomy.

Preoperative neck ultrasound is essential for all patients with thyroid nodules. The size of the thyroid gland along with the number, location, and size of thyroid nodules and the relationship between the nodules and thyroid and the surrounding cervical structures should be noted. FNA is the diagnostic procedure of choice for thyroid nodules to guide further therapy and inform surgical management. The 2015 ATA guidelines [11] recommend that an FNA be performed for those nodules with high and intermediate suspicion sonographic appearance that are >1 cm, low suspicion sonographic appearance >1.5 cm, and very low suspicion appearance >2 cm. FNA is not recommended for nodules with a benign sonographic appearance. High suspicion features (Fig. 12.1) are solid hypoechoic nodules with one or more of the following features: irregular margins, microcalcifications, taller-than-wide shape, rim calcifications with extrusive soft tissue component, or evidence of extrathyroidal extension. The estimated risk of malignancy for these nodules is 70–90%. Intermediate suspicion features (Fig. 12.2) are hypoechoic nodules with smooth margins without microcalcifications, extrathyroidal extension, or taller-than-wide shape. The estimated risk of malignancy for these nodules is 10–20%. Low suspicion features (Fig. 12.3) are iso- or hyperechoic solid nodules or partially cystic nodules without microcalcifications, irregular margins, extrathyroidal extension, or taller-than-wide shape. The estimated risk of malignancy for these nodules is 5–10%. Very

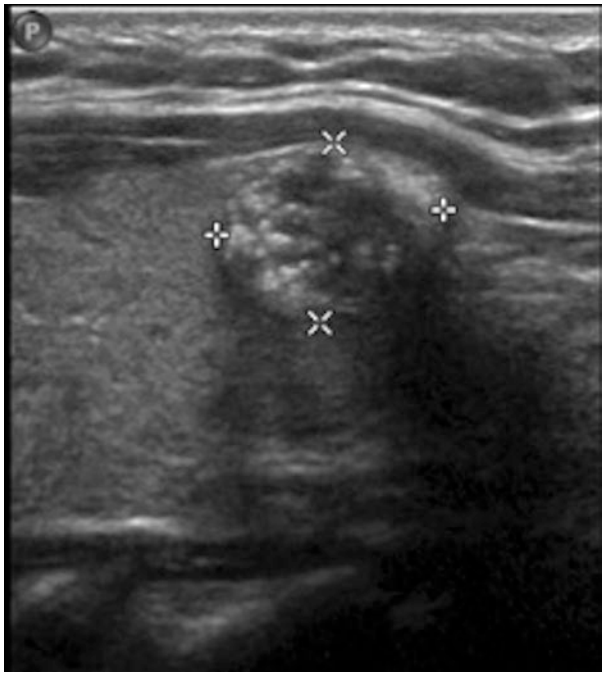

Fig. 12.1 High suspicion thyroid nodule with hypoechoic appearance and microcalcifications

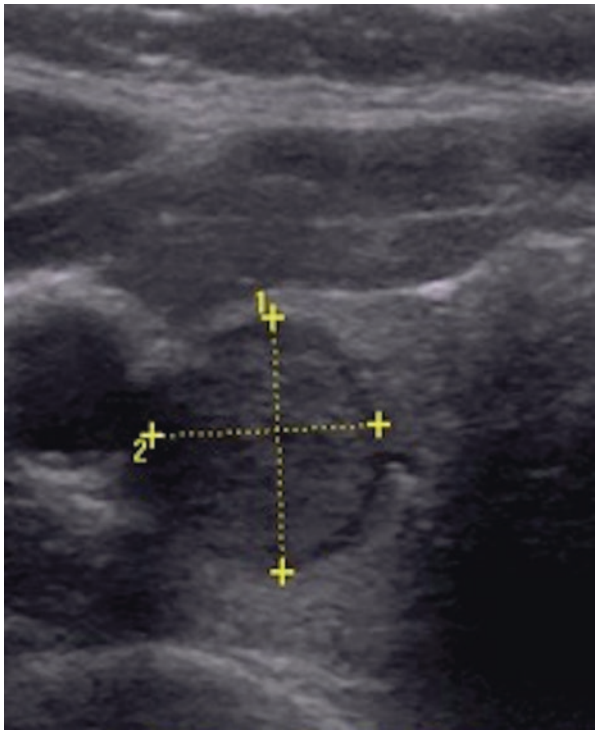

Fig. 12.2 Intermediate suspicion thyroid nodule with hypoechoic appearance and smooth borders

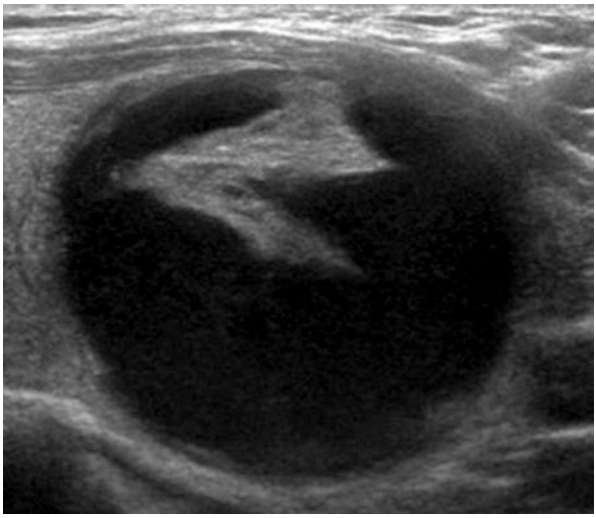

Fig. 12.3 Low suspicion thyroid nodule with partially cystic appearance with an eccentric solid component

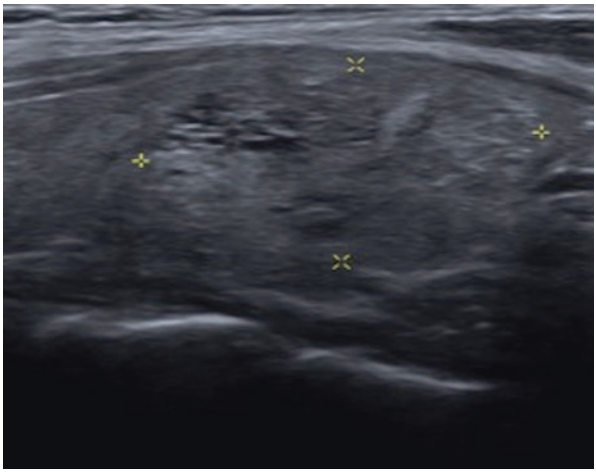

Fig. 12.4 Very low suspicion thyroid nodule with spongiform appearance

low suspicion features (Fig. 12.4) are spongiform appearance and the absence of any of the suspicious features mentioned above. The risk of malignancy is <3%. Benign features (Fig. 12.5) are purely cystic nodules, with a risk of malignancy of <1%.

For patients with known thyroid cancer or cytology and/or molecular findings suspicious for malignancy, lymph node mapping with ultrasound should be performed of the central and lateral neck compartments to evaluate for lymph node metastases. An FNA should be performed on lymph nodes ≥8 mm with any imaging features that are suspicious for malignancy, which include microcalcifications, cystic component, peripheral vascularity, round shape, and hyper-echogenecity (Fig. 12.6). Thyroglobulin washout of the FNA aspirate should be performed for indeterminate cytology to improve the accuracy of FNA for differentiated thyroid cancer. A thyroglobulin concentration <1 ng/mL is reassuring for benign disease,

Fig. 12.5 Benign cystic thyroid nodule with comet tail artifact from colloid

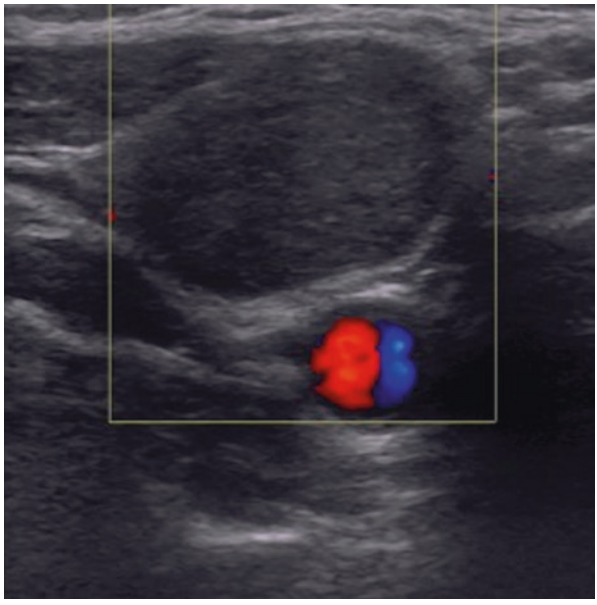

Fig. 12.6 Ultrasound of enlarged hyperechoic lateral compartment lymph node suspicious for metastases

but optimal values for the identification of malignancy are less clear. A meta-analysis by Pak et al. pooling eight studies evaluating the optimal cutoff value for thyroglobulin washout determined that the optimal cutoff was 32 ng/mL for discriminating between benign and malignant lymph nodes [16]. Cross-sectional imaging with CT is not indicated except for goiters that are suspected to extend into the mediastinum or retropharyngeal space where ultrasound is limited or for locally advanced cancers with posterior extension or associated with bulky lymphadenopathy (Fig. 12.7). In these situations, intravenous contrast is essential to evaluate for invasion into the aerodigestive tract, nerves, and major blood vessels and to facilitate operative planning.

All patients with subjective or objective voice changes, a prior history of anterior cervical or chest surgery, or locally advanced cancer should be evaluated with laryn-

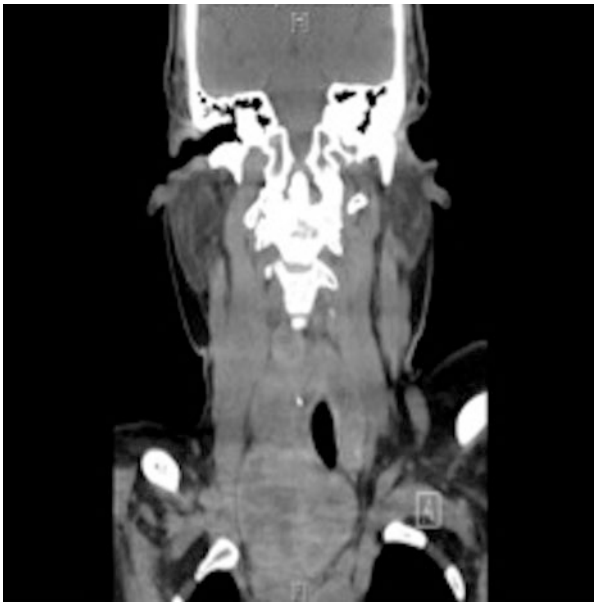

Fig. 12.7 Computed tomography demonstrating substernal thyroid extension

goscopy to assess vocal cord function. A paralyzed vocal cord significantly increases the risk of surgery and may alter surgical planning. Surgery on the side contralateral to the paralyzed vocal cord should be undertaken with caution because the patient is at increased risk for bilateral vocal cord paralysis and subsequent tracheostomy.

Fine Needle Aspiration/Molecular Testing

The management of thyroid nodules is largely directed by the cytologic findings from FNA; however, these results must be considered in the context of ultrasound and clinical findings. Results from FNA should be reported using the Bethesda classification system (Table 12.1), which recognizes six different categories and provides an estimation of malignancy for each category [17]. The risk of malignancy for each Bethesda category may vary between institutions, such that clinicians should be aware of the risk of malignancy at their own institutions for each cytologic category in order to make the most informed decisions for treatment [18]. Generally, the majority of thyroid nodules have benign (Bethesda category II) cytology (75%), a small proportion have malignant (Bethesda category VI) cytology (2–5%), while the remainder (20–30%) have indeterminate cytology. Indeterminate cytology includes atypia of undetermined significance (AUS)/follicular lesion of undetermined significance (FLUS) (Bethesda category III), follicular neoplasm (FN) (Bethesda category IV), and suspicious for malignancy (SM) (Bethesda category V).

Molecular testing may be performed for indeterminate nodules to supplement clinical and sonographic findings and provide further risk stratification. One option for molecular testing is the use of a gene expression classifier that analyzes 167 genes from

Table 12.1 Bethesda system for reporting thyroid cytology

Diagnostic criteria		Estimated risk of malignancy (%)
I	Nondiagnostic	1–4
II	Benign	0–3
III	Atypia of undetermined significance of follicular lesion of undetermined significance	5–15
IV	Follicular lesion or suspicious for a follicular lesion	15–30
V	Suspicious for malignancy	60–75
VI	Diagnostic for malignancy	97–99

an indeterminate nodule and compares them to the gene signatures of benign and malignant lesions using a proprietary algorithm to classify the nodule as either benign or suspicious. The gene expression classifier test was validated for 265 nodules with indeterminate cytology [19]. The negative predictive value (NPV) for AUS/FLUS and FN was 95% and 94%, respectively, which is similar to benign cytology results; therefore, many argue that it is sufficient to "rule out" malignancy. On the other hand, the NPV for Bethesda V lesions was only 85%, which is thought to be inadequate to exclude malignancy. The positive predictive value (PPV) for suspicious results was only 38% for AUS/FLUS and 37% for FN, making it insufficient to "rule in" malignancy. Another molecular approach is to evaluate the FNA aspirate for a panel of seven gene mutations or rearrangements (including BRAF, RAS, RET/PTC, and PAX8/PPARG translocation) associated with thyroid cancer. A single-center prospective study by Nikiforov et al. [20] analyzed 513 cytologically indeterminate nodes with the seven gene mutation panel and definitive histopathological assessment. The BRAF, RET/PTC, and PAX8/PPARG mutations were associated with 100% risk of malignancy, while the RAS mutation carried an 85% risk of cancer. The nonmalignant RAS-positive nodules were all follicular adenomas. Based on the high likelihood of malignancy, the authors suggested that patients with a positive BRAF, RET/PTC, and/or PAX8/PPARG mutation should undergo definitive thyroid cancer treatment and could avoid a diagnostic lobectomy and two-stage thyroidectomy (lobectomy followed by completion thyroidectomy). However, the low sensitivity for malignancy of the seven gene panel is felt to be inadequate to support surveillance for negative results. More recently, next-generation DNA sequencing for an expanded panel of genes has shown promising results, with a 90% sensitivity and 92% specificity for FN [21] and 91% sensitivity and 92% specificity for AUS/FLUS [22], but this has not yet been validated.

Surgical Management of Papillary Thyroid Cancer

There has been a long-standing controversy regarding the extent of surgery for patients with PTC and whether thyroid lobectomy or total thyroidectomy is superior (Table 12.2). Proponents of thyroid lobectomy argue that PTC is an indolent disease with an excellent prognosis, and the higher risks for recurrent laryngeal nerve injury

Table 12.2 Extent of surgery: reasons for/against total thyroidectomy for papillary thyroid cancer

For	Against
Regional or distant metastases	Localized tumor
Addresses multifocal and/or bilateral disease	Increased risk of RLN injury, hypoparathyroidism
Facilitates surveillance with Tg and/or imaging	Indolent disease that does not imply a significant risk of mortality, recurrence
Need for postoperative RAI	Requires lifelong thyroid hormone replacement

RAI radioactive iodine, *Tg* thyroglobulin, *RLN* recurrent laryngeal nerve

and hypoparathyroidism associated with thyroidectomy are not justified since there is not a clear survival benefit [23, 24]. In many patients, the need for lifelong thyroid hormone replacement may be avoided with lobectomy. Advocates for total thyroidectomy argue that surgery can be performed safely, and complete resection of the thyroid addresses the risks of multifocal and bilateral disease, facilitates treatment with radioactive iodine, and simplifies surveillance [25]. The 2015 ATA Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer [11] recommend that patients with PTC measuring between 1 and 4 cm may be treated with either thyroid lobectomy or total thyroidectomy. Prior versions of these ATA guidelines [26] had recommended total thyroidectomy for PTC measuring >1 cm. This recommendation was based primarily on a study by Bilimoria et al. [27] using the National Cancer Database (NCDB) that included 52,173 patients with PTC demonstrating a slightly higher 10-year survival for total thyroidectomy vs thyroid lobectomy (98.4% vs 97.1%, respectively, $p < 0.05$). Several factors that could impact survival, including extrathyroidal extension, completeness of resection, and patient comorbidities, were not available for this study. A more contemporary NCDB study by Adam et al. [28] that included 61,775 patients with PTC accounted for these and other risk factors and found no survival advantage associated with total thyroidectomy compared to thyroid lobectomy for patients with tumors 1–4 cm in size, suggesting that thyroid lobectomy is an effective treatment for low-risk differentiated thyroid cancer. Another study using the Surveillance, Epidemiology, and End Results (SEER) database that included 22,724 patients with PTC also revealed no difference in survival between thyroid lobectomy and total thyroidectomy [29]. Since PTC is frequently multifocal, some studies have reported a lower risk of locoregional recurrence after total thyroidectomy [30]. However, in a retrospective study by Vaisman et al. [31] of 289 patients treated with thyroid lobectomy ($n = 72$) or total thyroidectomy ($n = 217$), there was no difference in structural recurrence between the lobectomy and total thyroidectomy groups (4.2% vs 2.3%, respectively; $p > 0.05$). There were no patients who died from thyroid cancer. Importantly, 88% of patients who recurred were rendered free of disease with additional therapy, suggesting that locoregional recurrence rates are low after lobectomy with proper patient selection and that recurrences can be treated without detriment to survival.

Based on these studies, the 2015 ATA guidelines recommended a more individualized approach to treatment, taking into consideration tumor features, patient characteristics, patient preference, and surgeon experience. The ATA has devised a risk

Table 12.3 ATA 2015 risk stratification system

ATA low risk	Papillary thyroid cancer with all of the following:
	– No distant metastases
	– No tumor invasion into local structures
	– No aggressive histology (tall cell, columnar, hobnail)
	– No vascular invasion
	– Clinical N0 or ≤5 lymph node micrometastases (<0.2 cm)
	Intrathyroidal encapsulated follicular variant of PTC
	Intrathyroidal well-differentiated FTC with capsular invasion and no/minimal vascular invasion (≤4 foci)
	Intrathyroidal papillary microcarcinoma, unifocal or multifocal
ATA intermediate risk	Microscopic invasion of tumor into perithyroidal soft tissue
	PTC with vascular invasion
	Clinical N1 or >5 pathologic lymph node metastases <3 cm
	Multifocal papillary microcarcinoma with ETE and BRAF mutated
	Aggressive histology (tall cell, columnar, hobnail)
ATA high risk	Macroscopic invasion of tumor into perithyroidal soft tissue
	Incomplete tumor resection
	Distant metastases
	Postoperative serum thyroglobulin suggestive of distant metastases
	Pathologic lymph node metastases ≥3 cm
	FTC with extensive vascular invasion (>4 foci)

PTC papillary thyroid cancer, *FTC* follicular thyroid cancer, *ETE* extrathyroidal extension

stratification scheme that categorizes patients into low-, intermediate-, and high-risk categories for recurrence that should be incorporated into treatment decisions [11] (Table 12.3). Patients with intermediate- or high-risk tumors (tumors that are >4 cm or with gross extrathyroidal extension, clinically apparent lymph node metastases, distant metastases, aggressive histological variants, and vascular invasion) should undergo a total thyroidectomy to enable radioactive iodine treatment and reduce the risk for recurrence and facilitate surveillance [32]. Regardless of tumor size, patients with a history of radiation exposure to the head and neck or familial thyroid cancer, or with bilateral thyroid nodules, should be considered for total thyroidectomy, since they are at risk for multifocal/bilateral cancer [11, 33]. Patients who have tumors between 1 and 4 cm without intermediate- or high-risk features are at low risk for recurrence and unlikely to need treatment with radioactive iodine; therefore, they may be treated with either thyroid lobectomy or total thyroidectomy. The decision for extent of surgery in these patients should be based on the overall treatment plan ideally formulated by a multidisciplinary team taking into consideration the individual risks/benefits of surgery, overall treatment goals, and patient preference. If thyroid lobectomy is selected, the patient should be informed (and consented) that if high-risk tumor features are identified during surgery (i.e., macroscopic extrathyroidal extension or metastatic lymph nodes), total thyroidectomy may be performed. Similarly, if high-risk tumor features are identified on final pathology, completion thyroidectomy should be performed.

If a FNA is suspicious for PTC (Bethesda V), there is a 60–75% risk of malignancy. Due to the high risk, these patients should be treated similarly to patients with a FNA diagnostic of malignancy (Bethesda VI), with either thyroid lobectomy or total thyroidectomy. Alternatively, a diagnostic lobectomy with frozen section/touch prep may be performed to determine if the tumor is malignant. If the intraoperative assessment confirms malignancy, a definitive oncological operation may be performed with either lobectomy or total thyroidectomy. If frozen section/touch prep is not definitive for malignancy, the operation should be terminated and the decision for completion thyroidectomy based on final pathology results.

For tumors <1 cm without lymph node metastases or other high-risk features, thyroid lobectomy is recommended, except if there are other indications for total thyroidectomy (history of radiation exposure to the head and neck, history of familial thyroid cancer, or the presence of bilateral thyroid nodules). Alternatively, active surveillance can be considered for these very low-risk tumors. A study from Japan by Ito et al. [34] evaluated nonoperative management among 1235 patients with papillary microcarcinoma with a mean follow-up of 75 months. At 10 years, only 6.8% of patients progressed to develop clinically significant disease, which was defined as an increase in tumor size to 12 mm or development of lymph node metastases. Disease progression at 10 years was observed in 22.5%, 4.5%, and 2.5% of patients who were aged <40, 40–60, and >60 years, respectively. None of the patients in the study developed distant metastases or died of PTC. Nonoperative management of sub-centimeter PTC with surveillance may be considered as an alternative to surgery for those patients at high risk for surgery due to severe comorbidities, those who have limited life expectancy, or those who are of advanced age.

The relationship between surgeon volume and patient outcomes after thyroidectomy has been extensively studied. Published studies have consistently demonstrated that surgeons who perform more thyroidectomies have superior outcomes, on average, with fewer complications and lower costs. Sosa et al. [35] analyzed the effect of surgeon volume on patient outcomes in 5860 patients who underwent total thyroidectomy in Maryland from 1991 to 1996. After adjustment for case mix and hospital volume, surgeon volume of >100 cases was associated with lower complication rates, shorter hospital stay, and lower cost. In a national study of 16,954 patients who underwent total thyroidectomy, Adam et al. [36] looked for a surgeon volume threshold using multivariate modeling and restrictive cubic spines. The study demonstrated that the likelihood of experiencing a complication decreased with increasing surgeon volume until surgeons performed >25 thyroidectomies per year. Complication rates were on average 51% higher when surgery was performed by low-volume surgeons. Based on these results, the authors defined high-volume thyroid surgeons as those who perform >25 total thyroidectomies per year, which has important implications for quality improvement and identification of criteria for referral. In areas where referral to high-volume surgeons is problematic, a surgeon could be identified to perform all the thyroidectomies in order to concentrate surgeon experience and facilitate improved patient outcomes.

A therapeutic central (Level VI) lymph node dissection (CLND) is recommended for patients with PTC who have clinically involved lymph nodes identified on either

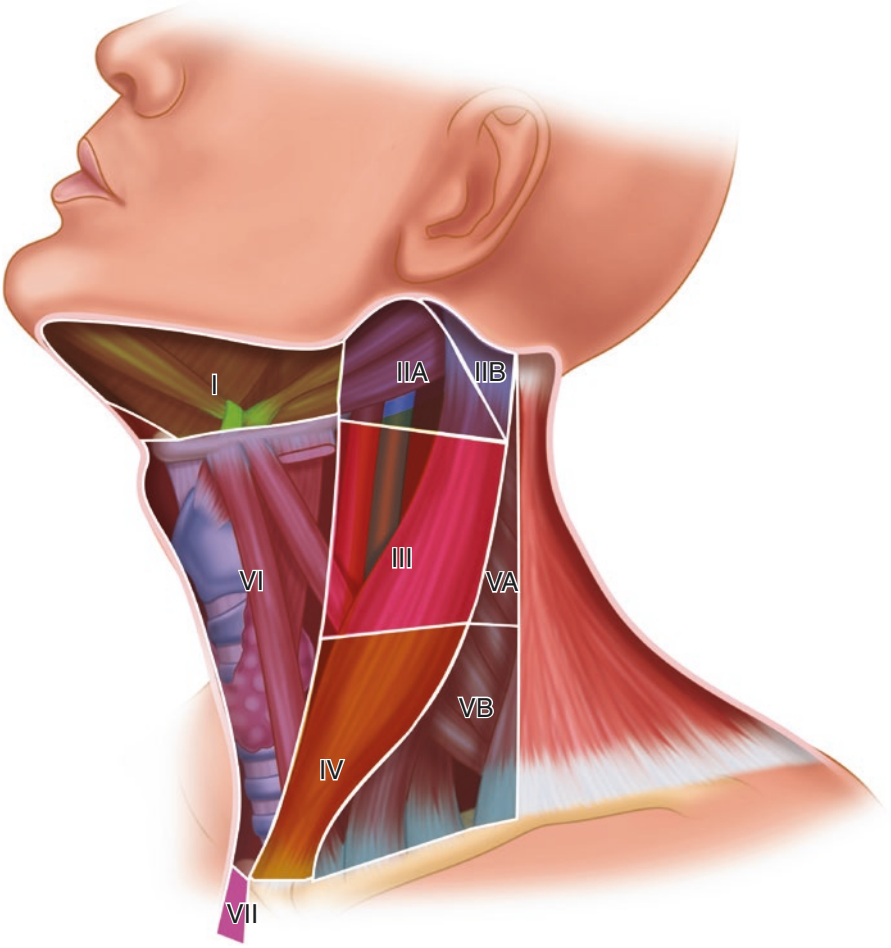

Fig. 12.8 Lymph node compartments in the neck

preoperative imaging or physical examination or intraoperatively. The ATA published a Consensus Statement on the Terminology and Classification of Central Neck Dissection in 2009 to standardize the surgical approach to the central neck [37]. A complete CLND should extirpate all lymph nodes within the central compartment, for which the anatomic boundaries are the hyoid superiorly, innominate artery inferiorly, and carotid arteries laterally (Fig. 12.8). There is no role for "berry picking" of clinically involved lymph nodes, since recurrence after non-compartment-oriented dissection is increased, along with the likelihood of requiring a higher-risk, remedial operation. The role of prophylactic CLND (pCLND) for patients without clinically evident lymph node metastases is controversial. Prophylactic CLND has been suggested to decrease locoregional recurrence and postoperative thyroglobulin levels, provide more accurate staging, and inform

radioactive iodine use [38]. However, pCLND has not been shown to be associated with improved survival, and it is associated with an increased chance of temporary recurrent laryngeal nerve injury and hypoparathyroidism [39]. A meta-analysis by Wang et al. [40] of studies evaluating pCLND revealed no difference in long-term complications or recurrence between patients who underwent total thyroidectomy alone or total thyroidectomy with pCLND. There was a trend toward lower recurrence among patients who underwent pCLND; however, 31 patients would have to be treated with pCLND in order to avoid one recurrence, suggesting that any benefit of pCLND would be small and observed only in high-volume surgical practices. The 2015 ATA guidelines for differentiated thyroid cancer recommend that prophylactic CLND be considered for advanced primary tumors (T3 or T4), or for tumors with clinically involved lateral compartment lymph nodes, and that thyroidectomy without prophylactic CLND dissection is appropriate for low-risk (T1 and T2) tumors [11]. If suspicious lateral compartment lymph nodes are identified on preoperative ultrasound, an FNA is recommended, and if the FNA is positive for malignancy, a lateral compartment lymph node dissection of levels IIa, III, IV, and Vb (Fig. 12.8) should be performed with preservation of the internal jugular vein, sternocleidomastoid muscle, and spinal accessory nerve. The ATA published a Consensus Review and Statement Regarding the Anatomy, Terminology, and Rationale for Lateral Neck Dissection in Differentiated Thyroid Cancer in 2012 [41]. There is no role for prophylactic lateral compartment lymph node dissection for PTC.

Indeterminate Nodules

The goal of thyroid surgery for indeterminate thyroid nodules is to establish a definitive diagnosis while minimizing the risk of surgery and, if possible, perform the appropriate oncological operation up front if a diagnosis of malignancy can be established. Patients should be consented for a possible total thyroidectomy if a definitive diagnosis of malignancy is established during surgery and indications for total thyroidectomy are present, including such high-risk tumor features as extrathyroidal extension or lymph node metastases. An up-front total thyroidectomy should be performed for indeterminate lesions if the patient has a prior history of radiation exposure to the thyroid or a history concerning for familial thyroid cancer and if clinically significant nodules are present in the contralateral thyroid lobe. Intraoperative frozen section/touch prep analyses are not routinely recommended for indeterminate nodules as they are seldom helpful. In a study by Chen et al. [42], 120 patients with follicular neoplasms on FNA were treated with thyroid lobectomy with intraoperative frozen section. Frozen section only identified malignancy in 4 patients (3.3%), nondiagnostic in 104 patients (87%), and falsely positive in 6 patients (5%). A cost analysis by Zanocco et al. [43] comparing intraoperative frozen section for follicular neoplasms vs thyroid lobectomy alone revealed that intraoperative frozen section was not cost-effective. Frozen section/touch prep is unable

to evaluate for capsular or vascular invasion to diagnose follicular/Hurthle cell cancer so should be reserved for situations when there are clinical features that are highly suspicious for malignancy, such as extrathyroidal extension or lymph node metastases.

Patients with AUS/FLUS (Bethesda category III) lesions may be treated with a diagnostic lobectomy, repeat cytology with molecular testing, or surveillance. In addition to the cytological results, the decision for management should take into consideration the sonographic appearance of the nodule, clinical context, and patient preference. While the risk of malignancy for AUS/FLUS should range from 5 to 15%, evaluation of the sonographic pattern of the nodules is helpful to further risk stratify AUS/FLUS nodules. In a study of 155 nodules with AUS/FLUS cytology, nodules were classified by ATA sonographic pattern [44]. Only 8% of nodules with very low-risk sonographic features were malignant, while 58% with low or intermediate risk and 100% with high-risk appearances were malignant. This should be taken in the context that the overall risk of malignancy for AUS cytology in this study was 70%. In another study with an overall lower risk of malignancy of 22% for AUS cytology, 70% of nodules with high-risk sonographic appearance were malignant [45]. Based on these data, thyroid lobectomy should be considered strongly for patients with suspicious-appearing nodules on ultrasound. For nodules without high-risk sonographic appearance, repeat FNA with or without molecular testing may be helpful to further risk stratify the nodule and guide treatment, and clinical context and patient preference should be taken into consideration. Alternatively, surveillance with ultrasound may be employed, particularly for nodules with very low-risk sonographic appearance and/or nodules in patients with high surgical risk. Thyroid lobectomy should be considered for nodules that increase in size or take on suspicious ultrasound features during surveillance.

Thyroid nodules with follicular/Hurthle cell neoplasm (FN) (Bethesda category IV) cytology have, on average, a 15–30% risk of malignancy. Thyroid lobectomy has been the long-standing treatment for these patients. However, for patients who would like to avoid surgery and who have tumors with low-risk imaging and clinical features, molecular testing may be performed to provide further risk stratification. If molecular testing is indeterminate, thyroid lobectomy is recommended.

The risk of malignancy for a Hurthle cell neoplasm on cytology is 15–45%. Hurthle cell neoplasms are treated like FN, with a diagnostic thyroid lobectomy. Unlike FN, Hurthle cell neoplasms are more likely to be malignant when they are larger in size. The risk of malignancy for nodules >4 cm exceeds 50%, so up-front total thyroidectomy can be recommended [46]. Molecular testing appears to be less effective for Hurthle cell neoplasms. In a study by Brauner et al. [47], 45 of 71 Hurthle cell neoplasms had suspicious gene expression classifier results. Only 14% (6/43) of the nodules were malignant on final histopathology (4 with Hurthle cell carcinoma and 2 with PTC).

If histopathology from thyroid lobectomy reveals that the tumor is an intermediate- or high-risk thyroid cancer, a completion thyroidectomy is recommended. Completion thyroidectomy is generally not recommended for low-risk thyroid cancers but may be considered based on the overall goal for treatment and patient pref-

erence. Prior to performing completion thyroidectomy, laryngoscopy should be performed to evaluate vocal cord function. A paralyzed vocal cord increases the risk of surgery and may alter surgical planning. The completion thyroidectomy should be performed either within 1 week or 2–3 months after the initial surgery to avoid the worst inflammation.

Benign Nodules

Benign thyroid nodules (Bethesda category II) typically do not require surgical resection but should be followed with ultrasound surveillance. If the nodule increases in size significantly (50% increase in nodule volume or >2 mm growth in 2+ dimensions), FNA should be repeated or diagnostic lobectomy performed based on the unique clinical scenario and patient preference. Surgical resection is recommended for benign nodules that are symptomatic due to compressive symptoms, such as dysphagia or dyspnea. Also, surgery may be considered for large asymptomatic nodules, when FNA may be less accurate. Several studies have shown that 10–12% of thyroid nodules >4 cm with benign cytology on FNA are malignant on final surgical pathology [48]. For nodules with nondiagnostic pathology, a repeat FNA should be performed with ultrasound guidance and on-site cytopathological assessment to increase the likelihood of adequacy. Thyroid lobectomy is recommended for nondiagnostic cytology if the nodule has high suspicion sonographic features or if cytology is repeatedly nondiagnostic.

Medullary Thyroid Cancer

Patients with an FNA suspicious for MTC should undergo immunohistochemical staining of the biopsy for calcitonin/CEA and calcitonin/CEA washout of the FNA aspirate [49], and serum calcitonin and CEA levels should be obtained. If immunohistochemistry or calcitonin washout establishes the diagnosis of MTC, the patients should be treated as if they have MTC. If these results are inconclusive or normal, a diagnostic lobectomy should be performed. Patients with FNA diagnostic for MTC should have a total thyroidectomy with bilateral level VI CLND due to the high frequency of lymph node metastases and lack of effective adjuvant therapy. In a study by Scollo et al. [50] of 54 patients with sporadic MTC, lymph node metastases were present in 30% of patients with tumors <1 cm, 50% of patients with tumors 1–3 cm, and 100% for patients with tumors that were >3 cm. A selective lateral compartment (Level II–V) lymph node dissection is recommended for biopsy-proven lymph node metastases. The role of prophylactic lateral compartment dissection for patients with elevated serum calcitonin levels but without biopsy-proven lateral compartment lymph node metastases is controversial. Some clinicians feel that prophylactic lateral compartment lymph node dissection should be performed

for serum calcitonin levels >20 pg/mL due to the high frequency of occult nodal metastases and improved chance of biochemical cure [51]. However, others feel that lateral compartment lymph node dissection should only be performed for biopsy-proven metastases. The 2015 ATA MTC Guidelines [13] "neither recommend for nor against" prophylactic lateral compartment lymph node dissection in patients with elevated calcitonin without distant metastases. For these patients, an individualized approach is recommended, taking into consideration patient age, comorbidities, overall treatment goals, and patient preference. Younger, healthy patients may be considered for a more aggressive approach with prophylactic lateral compartment dissection, while observation with serial ultrasounds may be preferred for older, less healthy patients and for those patients unwilling to accept the risk of complications from surgery if no metastatic lymph nodes ultimately are identified.

Hyperthyroidism

Patients with thyroid nodules and hyperthyroidism should be initially evaluated by obtaining a thyrotropin receptor antibody level or a radioiodine uptake scan to determine the etiology of hyperthyroidism, which may be Graves' disease, toxic multinodular goiter, toxic adenoma, or thyroiditis. FNA is not recommended for hyperfunctioning (hot) nodules, since these nodules are rarely malignant [52]. Nonfunctioning (cold) nodules should be treated according to the 2015 ATA guidelines for the management of thyroid nodules and should undergo FNA based on the sonographic pattern and size of the nodules. Thyroid cancer in the context of hyperthyroidism appears to be more aggressive compared to thyroid cancer in euthyroid patients [53]. In the USA, the majority of patients with nodular Graves' disease, toxic multinodular goiter, and toxic adenoma are treated with radioactive iodine; however, surgery is the preferred treatment for some patients. The 2016 ATA guidelines for the diagnosis and management of hyperthyroidism [10] recommended surgery for patients who are <5 years, are pregnant, fail alternative treatment, are unable to comply with radiation safety guidelines, have nodules that are concerning or diagnostic for malignancy, need rapid correction of the thyrotoxic state, patients with insufficient radioactive iodine uptake, with large (≥80 g) goiters causing compressive symptoms, with moderate to severe Graves' orbitopathy, or based on patient preference. For patients without clear indications for surgery, treatment with antithyroid drugs (methimazole), radioactive iodine, or surgery should be based on goals of treatment incorporating patient values and preference. Total thyroidectomy is the procedure of choice for Graves' disease or toxic multinodular goiter because subtotal thyroidectomy has similar morbidity but a higher risk of recurrent hyperthyroidism [54]. A thyroid lobectomy is recommended for a toxic adenoma. Prior to thyroidectomy, patients with hyperthyroidism should be rendered euthyroid to avoid thyroid storm during surgery. This can be accomplished with methimazole within 4–6 weeks. Propylthiouracil is no longer recommended due to a higher risk of hepatic failure [55]. Methimazole is typically started at 10–30 mg and titrated based

on response. Beta-blockers may be added to control tachycardia and tremor. Thyroidectomy can be performed safely once T3 and T4 are normal; TSH lags behind and does not need to be normal at the time of surgery. Patients with nodular Graves' disease should be treated with supersaturated potassium iodine (SSKI) with two drops three times daily starting 10 days prior to surgery in order to decrease vascularity of the thyroid gland and reduce blood loss [56]. This is not recommended for toxic multinodular goiter or toxic adenoma, since it may exacerbate hyperthyroidism in these patients. If surgery is chosen, patients should be referred to a high-volume surgeon, since high-volume surgeons on average have superior outcomes compared to low-volume surgeons [35, 36, 57]. The risks of thyroid surgery for hyperthyroidism are higher even than for thyroid cancer. In a nationwide study by Kandil et al. [57] of 46,261 patients between 2000 and 2009 using the Health Care Utilization Project National Inpatient Sample (HCUP-NIS), Graves' disease patients had the highest complication rate (17.5%) compared to patients undergoing total thyroidectomy for other benign (13.9%) and malignant (13.2%) thyroid disease ($p < 0.01$).

Patients with nodular Graves' disease who are treated with thyroidectomy are at higher risk for postoperative hypoparathyroidism and hypocalcemia. Preoperative supplementation with calcium and/or vitamin D may reduce the risk of postoperative hypocalcemia. In a study by Oltmann et al. [58], 45 patients with Graves' disease were treated with 1 g of calcium carbonate three times per day for 2 weeks prior to thyroidectomy and compared to 38 Graves' disease patients who underwent thyroidectomy without preoperative treatment. The rate of symptomatic hypocalcemia was higher in the untreated group (26 vs 9%, $p < 0.05$). In a retrospective study by Kim et al. [59] of 272 patients who underwent thyroidectomy, the incidence of postoperative hypocalcemia was 43.8% for patients who were vitamin D insufficient compared to 30.4% for those who were vitamin D sufficient (p-0.043). Based on such results, the 2016 ATA guidelines recommend vitamin D repletion prior to surgery for patients who are vitamin D insufficient and preoperative calcitriol supplementation in patients at increased risk for hypoparathyroidism.

Multinodular Goiter

Surgery is recommended for goiters that are symptomatic due to local compression, concern for malignancy, or for cosmetic reasons. Large goiters may compress the esophagus or trachea, leading to dysphagia or dyspnea. In select situations when many nodules meet the criteria for FNA, the patient or clinician may prefer surgery rather than surveillance despite benign FNA of select nodules. Surgery may also be performed if the patient is concerned about the cosmetic appearance of a large goiter, although it is rare that a patient with a very large goiter does not have at least some compressive symptoms. Total thyroidectomy is recommended if the goiter/nodules involve(s) both lobes of the thyroid; thyroid lobectomy is appropriate for a unilateral goiter.

Pediatric Patients

Thyroid nodules are less common in children than adults; however, nodules in children are more likely to be malignant (22–26% rate of malignancy for children vs 5% for adults) [60]. The 2015 ATA management guidelines for children with thyroid nodules and differentiated thyroid cancer [12] recommend that the initial evaluation and treatment of children with thyroid nodules should be similar to adults, with several exceptions. The decision to perform FNA should be based primarily on sonographic features (i.e., irregular margins, hypoechoic appearance, and microcalcifications) and clinical context rather than nodule size alone, since the size of the thyroid gland changes with age and absolute size of nodules does not predict malignancy. The risk of malignancy for children with nodules and indeterminate cytology is higher than in adults. In children, 28% of nodules with AUS/FLUS cytology and 58% with FN cytology are malignant on histopathology after surgical resection [61]. Accordingly, thyroid lobectomy is favored over repeat FNA and/or surveillance. Molecular testing to provide further risk stratification for indeterminate nodules has not been validated in children, so it is not recommended [12]. Also, all children with thyroid nodules should have ultrasonographic lymph node mapping and FNA of suspicious lymph nodes to evaluate for metastases, since there is a higher likelihood that these nodules are malignant. Similar to adults, FNA for hyperfunctioning nodules is not recommended; however, thyroid lobectomy is recommended over radioactive iodine due to the possible mutagenic effects of radioactive iodine on thyroid tissue in children [62]. Finally, for children with PTC, total thyroidectomy is recommended, since there is a 60% risk of multifocal disease, and total thyroidectomy has been shown to be associated with a reduction in the risk of recurrence [63]. The risk of postoperative complications after thyroidectomy is higher for children than adult patients. In a nationwide study by Sosa et al. [64] using HCUP-NIS of 1199 pediatric and 96,002 adult patients who underwent thyroidectomy, children were more likely to have endocrine-related complications than adults (9.1 vs 6.3%, respectively; $p < 0.01$). In another nationwide study by Tuggle et al. [65] using HCUP-NIS of 607 children who underwent endocrine neck procedures, high-volume surgeons (>30 cervical endocrine surgeries per year) compared to low-volume surgeons had shorter length of stay (1.5 vs 2.1, $p < 0.01$), lower costs ($12,474 vs $15,662, $p < 0.05$), and trended toward fewer complications (5.6 vs 10%, p = NS).

Pregnant Patients

The ATA published guidelines for the management of thyroid disease during pregnancy in 2011 [14]. Similar to nonpregnant adult patients, the evaluation of euthyroid pregnant patients should begin with a thyroid ultrasound. FNA of nodules with

suspicious sonographic features is recommended, while FNA of benign-appearing nodules may be deferred based on patient preference until the pregnancy comes to term. If surgery is indicated based on a cytology diagnostic for malignancy, the decision to perform surgery during pregnancy or after delivery must be individualized. In a study by Moosa et al. [66], the outcomes of 61 pregnant patients were compared to age-matched nonpregnant thyroid cancer patients. Outcomes were similar for pregnant and nonpregnant patients: recurrence 9 (15%) vs 107 (23%), respectively, distant recurrences 1 (2%) vs 12 (3%), and cancer deaths 0 vs 6 (1.2%) (all p = NS). Patients who had surgery after pregnancy had similar outcomes to patients who underwent surgery during pregnancy (2 [14%] vs 7 [15%] developed recurrences, p = NS). A nationwide study by Kuy et al. [67] using HCUP-NIS compared 201 pregnant patients to age-matched nonpregnant patients. Pregnant patients were more likely than nonpregnant patients to have endocrine-related complications (15.9 vs 8.1, respectively; $p < 0.01$), general complications (11.4 vs 3.6%, $p < 0.01$), and greater length of stay (2 vs 1 day, $p < 0.01$). The overall fetal and maternal complication rates were 5.5% and 4.5%, respectively. Based on this study and others demonstrating no difference in outcomes if surgery is delayed, most patients have surgery after delivery to minimize the risk to the patient and fetus. Elective surgery should be considered during the end of the second trimester for large or locally advanced primary tumors, extensive lymphadenopathy, aggressive histology including MTC, or if the tumor progresses early in pregnancy.

Alternative Access Thyroidectomy

Robotic-assisted thyroid surgery through either a transaxillary or axillo-breast approach avoids a cervical incision. The ideal patients for this approach have a small body habitus, low body mass index (BMI), and a normal-sized thyroid with small nodules (<3 cm) [68]. In addition to the usual complications associated with thyroid surgery, alternative access site surgery can be associated with chest wall numbness, brachial plexus injuries, pneumothorax, and skin flap perforation/necrosis. The vast majority of studies evaluating these techniques are from South Korea. Although there was initial enthusiasm for minimally invasive techniques for thyroidectomy in the USA, the technology has not been embraced outside of select centers. A meta-analysis by Sun et al. [69] included 11 studies with 726 patients undergoing robotic surgery and 1205 undergoing conventional thyroidectomy. The robotic group was younger (40.5 vs 49.2 years, respectively), had a lower BMI (23.1 vs 24.2), and was less likely to undergo total thyroidectomy (58.1 vs 75.1%). The tumors were small, with a mean size of 8 mm. Mean operative time was 77 min longer for the robotic group ($p < 0.001$). There was no significant difference between the groups in the frequency of RLN injury, hypoparathyroidism, postoperative hematoma, or seroma. The robotic group had higher cosmetic satisfaction scores, but follow-up was only 3 months.

Postoperative Management

After thyroidectomy, communication between members of the treatment team is essential to fully integrate care. Thyroidectomy is a well-tolerated procedure, with infrequent complications when performed by an experienced surgeon as measured by the number of thyroid procedures performed. After surgery, patients should be monitored for hematoma, voice changes, and hypocalcemia. Postoperative bleeding and hematoma are rare (<1%) but can be life threatening, with emergent loss of the airway. The presence of new onset hoarseness after surgery may be due to irritation from the endotracheal tube, vocal cord edema/hematoma, or recurrent laryngeal nerve (RLN) injury. Transient RLN injury is seen in 3% of patients, and permanent RLN injury is seen in 0.5–1% of patients after surgery performed by high-volume thyroid surgeons. Patients with significant dyspnea or symptoms concerning for aspiration should be referred for laryngoscopy to evaluate for vocal cord compromise. Hypoparathyroidism leading to hypocalcemia is the most common complication after thyroidectomy. Transient hypoparathyroidism is seen in 10–20% of patients and permanent hypoparathyroidism in 1–2% of patients after total thyroidectomy. Transient hypoparathyroidism usually resolves in 2 weeks but may take up to 6 months. Selective or routine calcium and calcitriol supplementation should be implemented to avoid hypocalcemia. Selective supplementation can be based on ionized calcium or corrected serum calcium values and change in these values between the evening of surgery and postoperative day 1 morning values. Alternatively, selective supplementation can be based on parathyroid hormone (PTH) levels; for example, a serum PTH can be obtained in the recovery room, and if it is >10 pg/mL, patients are given 1000 mg calcium carbonate BID for 1 week; for PTH <10 pg/mL, patients are given 0.25 mcg calcitriol BID in addition to 1000 mg of calcium carbonate TID. Postoperative PTH levels are less accurate for predicting hypocalcemia in hyperthyroid patients. Some surgeons choose to routinely supplement all patients following thyroidectomy with calcitriol 0.25 mcg BID and 1000 mg calcium carbonate TID, since routine supplementation has been shown to be more cost-effective than selective supplementation [70]. Regardless of the strategy, patients should be counseled to contact the surgical team for symptoms of hypocalcemia, such as perioral or distal extremity paresthesias. If these symptoms occur, supplementation may need to be increased. Calcitriol and calcium supplementation are titrated down over 1–2 weeks after surgery, as long as the patient does not experience symptoms of hypocalcemia.

Conclusion

Thyroidectomy remains the mainstay of treatment for indeterminate thyroid nodules, thyroid cancer, and thyroid nodules associated with symptoms of compression; it is an appealing option for some patients with functional thyroid nodules associated with hyperthyroidism. Management of indeterminate thyroid nodules

should take into consideration sonographic features, clinical context, and patient preference. The role of molecular testing continues to evolve and may be used to provide improved risk stratification for indeterminate nodules. For thyroid cancer, the extent of thyroid resection and lymph node management needs to be individualized, taking into consideration risk stratification schema, treatment guidelines, and patient values. Patients should be referred to high-volume thyroid surgeons to minimize their risk of sustaining a surgical complication.

References

1. Tunbridge WM, Evered DC, Hall R, Appleton D, Brewis M, Clark F, et al. The spectrum of thyroid disease in a community: the Whickham survey. Clin Endocrinol. 1977;7(6):481–93.
2. Tan GH, Gharib H. Thyroid incidentalomas: management approaches to nonpalpable nodules discovered incidentally on thyroid imaging. Ann Intern Med. 1997;126(3):226–31.
3. Jin J, McHenry CR. Thyroid incidentaloma. Best Pract Res Clin Endocrinol Metab. 2012;26(1):83–96.
4. Sosa JA, Hanna JW, Robinson KA, Lanman RB. Increases in thyroid nodule fine-needle aspirations, operations, and diagnoses of thyroid cancer in the United States. Surgery. 2013;154(6):1420–6, discussion 6–7.
5. Siegel R, Ma J, Zou Z, Jemal A. Cancer statistics, 2014. CA Cancer J Clin. 2014;64(1):9–29.
6. Ahn HS, Kim HJ, Welch HG. Korea's thyroid-cancer "epidemic"–screening and overdiagnosis. N Engl J Med. 2014;371(19):1765–7.
7. Leenhardt L, Grosclaude P, Cherie-Challine L, Thyroid CC. Increased incidence of thyroid carcinoma in France: a true epidemic or thyroid nodule management effects? Report from the French Thyroid Cancer Committee. Thyroid. 2004;14(12):1056–60.
8. Morris LG, Myssiorek D. Improved detection does not fully explain the rising incidence of well-differentiated thyroid cancer: a population-based analysis. Am J Surg. 2010;200(4):454–61.
9. Kitahara CM, Sosa JA. The changing incidence of thyroid cancer. Nat Rev Endocrinol. 2016;12(11):646–53.
10. Ross DS, Burch HB, Cooper DS, Greenlee MC, Laurberg P, Maia AL, et al. 2016 American Thyroid Association guidelines for diagnosis and management of hyperthyroidism and other causes of thyrotoxicosis. Thyroid. 2016;26(10):1343–421.
11. Haugen BR, Alexander EK, Bible KC, Doherty GM, Mandel SJ, Nikiforov YE, et al. 2015 American Thyroid Association management guidelines for adult patients with thyroid nodules and differentiated thyroid cancer: The American thyroid association guidelines task force on thyroid nodules and differentiated thyroid cancer. Thyroid. 2016;26(1):1–133.
12. LaFranchi SH. Inaugural management guidelines for children with thyroid nodules and differentiated thyroid cancer: children are not small adults. Thyroid. 2015;25(7):713–5.
13. Wells SA Jr, Asa SL, Dralle H, Elisei R, Evans DB, Gagel RF, et al. Revised American Thyroid Association guidelines for the management of medullary thyroid carcinoma. Thyroid. 2015;25(6):567–610.
14. Stagnaro-Green A, Abalovich M, Alexander E, Azizi F, Mestman J, Negro R, et al. Guidelines of the American Thyroid Association for the diagnosis and management of thyroid disease during pregnancy and postpartum. Thyroid. 2011;21(10):1081–125.
15. Eng C, Mulligan LM, Smith DP, Healey CS, Frilling A, Raue F, et al. Low frequency of germline mutations in the RET proto-oncogene in patients with apparently sporadic medullary thyroid carcinoma. Clin Endocrinol. 1995;43(1):123–7.
16. Pak K, Suh S, Hong H, Cheon GJ, Hahn SK, Kang KW, et al. Diagnostic values of thyroglobulin measurement in fine-needle aspiration of lymph nodes in patients with thyroid cancer. Endocrine. 2015;49(1):70–7.

17. Cibas ES, Ali SZ. The Bethesda system for reporting thyroid cytopathology. Am J Clin Pathol. 2009;132(5):658–65.
18. Bongiovanni M, Spitale A, Faquin WC, Mazzucchelli L, Baloch ZW. The Bethesda system for reporting thyroid cytopathology: a meta-analysis. Acta Cytol. 2012;56(4):333–9.
19. Alexander EK, Kennedy GC, Baloch ZW, Cibas ES, Chudova D, Diggans J, et al. Preoperative diagnosis of benign thyroid nodules with indeterminate cytology. N Engl J Med. 2012;367(8):705–15.
20. Nikiforov YE, Ohori NP, Hodak SP, Carty SE, LeBeau SO, Ferris RL, et al. Impact of mutational testing on the diagnosis and management of patients with cytologically indeterminate thyroid nodules: a prospective analysis of 1056 FNA samples. J Clin Endocrinol Metab. 2011;96(11):3390–7.
21. Nikiforov YE, Carty SE, Chiosea SI, Coyne C, Duvvuri U, Ferris RL, et al. Highly accurate diagnosis of cancer in thyroid nodules with follicular neoplasm/suspicious for a follicular neoplasm cytology by ThyroSeq v2 next-generation sequencing assay. Cancer. 2014;120(23):3627–34.
22. Nikiforov YE, Carty SE, Chiosea SI, Coyne C, Duvvuri U, Ferris RL, et al. Impact of the multi-gene thyroseq next-generation sequencing assay on cancer diagnosis in thyroid nodules with atypia of undetermined significance/follicular lesion of undetermined significance cytology. Thyroid. 2015;25(11):1217–23.
23. Nixon IJ, Ganly I, Patel SG, Palmer FL, Whitcher MM, Tuttle RM, et al. Thyroid lobectomy for treatment of well differentiated intrathyroid malignancy. Surgery. 2012;151(4):571–9.
24. Matsuzu K, Sugino K, Masudo K, Nagahama M, Kitagawa W, Shibuya H, et al. Thyroid lobectomy for papillary thyroid cancer: long-term follow-up study of 1,088 cases. World J Surg. 2014;38(1):68–79.
25. Kebebew E, Clark OH. Differentiated thyroid cancer: “complete” rational approach. World J Surg. 2000;24(8):942–51.
26. Cooper DS, Doherty GM, Haugen BR, Kloos RT, et al. Revised American Thyroid Association management guidelines for patients with thyroid nodules and differentiated thyroid cancer. Thyroid. 2009;19(11):1167–214.
27. Bilimoria KY, Bentrem DJ, Ko CY, Stewart AK, Winchester DP, Talamonti MS, et al. Extent of surgery affects survival for papillary thyroid cancer. Ann Surg. 2007;246(3):375–81, discussion 81–4.
28. Adam MA, Pura J, Gu L, Dinan MA, Tyler DS, Reed SD, et al. Extent of surgery for papillary thyroid cancer is not associated with survival: an analysis of 61,775 patients. Ann Surg. 2014;260(4):601–5, discussion 5–7.
29. Mendelsohn AH, Elashoff DA, Abemayor E, St John MA. Surgery for papillary thyroid carcinoma: is lobectomy enough? Arch Otolaryngol Head Neck Surg. 2010;136(11):1055–61.
30. Grant CS, Hay ID, Gough IR, Bergstralh EJ, Goellner JR, McConahey WM. Local recurrence in papillary thyroid carcinoma: is extent of surgical resection important? Surgery. 1988;104(6):954–62.
31. Vaisman F, Shaha A, Fish S, Michael TR. Initial therapy with either thyroid lobectomy or total thyroidectomy without radioactive iodine remnant ablation is associated with very low rates of structural disease recurrence in properly selected patients with differentiated thyroid cancer. Clin Endocrinol. 2011;75(1):112–9.
32. Hay ID, Thompson GB, Grant CS, Bergstralh EJ, Dvorak CE, Gorman CA, et al. Papillary thyroid carcinoma managed at the Mayo Clinic during six decades (1940–1999): temporal trends in initial therapy and long-term outcome in 2444 consecutively treated patients. World J Surg. 2002;26(8):879–85.
33. Mazzaferri EL, Kloos RT. Clinical review 128: current approaches to primary therapy for papillary and follicular thyroid cancer. J Clin Endocrinol Metab. 2001;86(4):1447–63.
34. Ito Y, Miyauchi A, Kihara M, Higashiyama T, Kobayashi K, Miya A. Patient age is significantly related to the progression of papillary microcarcinoma of the thyroid under observation. Thyroid. 2014;24(1):27–34.

35. Sosa JA, Bowman HM, Tielsch JM, Powe NR, Gordon TA, Udelsman R. The importance of surgeon experience for clinical and economic outcomes from thyroidectomy. Ann Surg. 1998;228(3):320–30.
36. Adam MA, Thomas S, Youngwirth L, Hyslop T, Reed SD, Scheri RP, et al. Is there a minimum number of thyroidectomies a surgeon should perform to optimize patient outcomes? Ann Surg. 2016;265:402–7.
37. American Thyroid Association Surgery Working Group, American Association of Endocrine Surgeons, American Academy of Otolaryngology-Head and Neck Surgery, American Head and Neck Society, et al. Consensus statement on the terminology and classification of central neck dissection for thyroid cancer. Thyroid. 2009;19(11):1153–8.
38. White ML, Gauger PG, Doherty GM. Central lymph node dissection in differentiated thyroid cancer. World J Surg. 2007;31(5):895–904.
39. Giordano D, Valcavi R, Thompson GB, Pedroni C, Renna L, Gradoni P, et al. Complications of central neck dissection in patients with papillary thyroid carcinoma: results of a study on 1087 patients and review of the literature. Thyroid. 2012;22(9):911–7.
40. Wang TS, Cheung K, Farrokhyar F, Roman SA, Sosa JA. A meta-analysis of the effect of prophylactic central compartment neck dissection on locoregional recurrence rates in patients with papillary thyroid cancer. Ann Surg Oncol. 2013;20(11):3477–83.
41. Stack BC Jr, Ferris RL, Goldenberg D, Haymart M, Shaha A, Sheth S, et al. American Thyroid Association consensus review and statement regarding the anatomy, terminology, and rationale for lateral neck dissection in differentiated thyroid cancer. Thyroid. 2012;22(5):501–8.
42. Chen H, Nicol TL, Udelsman R. Follicular lesions of the thyroid. Does frozen section evaluation alter operative management? Ann Surg. 1995;222(1):101–6.
43. Zanocco K, Heller M, Elaraj D, Sturgeon C. Cost effectiveness of intraoperative pathology examination during diagnostic hemithyroidectomy for unilateral follicular thyroid neoplasms. J Am Coll Surg. 2013;217(4):702–10.
44. Gweon HM, Son EJ, Youk JH, Kim JA. Thyroid nodules with Bethesda system III cytology: can ultrasonography guide the next step? Ann Surg Oncol. 2013;20(9):3083–8.
45. Rosario PW. Thyroid nodules with atypia or follicular lesions of undetermined significance (Bethesda category III): importance of ultrasonography and cytological subcategory. Thyroid. 2014;24(7):1115–20.
46. Phitayakorn R, McHenry CR. Follicular and Hurthle cell carcinoma of the thyroid gland. Surg Oncol Clin N Am. 2006;15(3):603–23, ix-x.
47. Brauner E, Holmes BJ, Krane JF, Nishino M, Zurakowski D, Hennessey JV, et al. Performance of the Afirma gene expression classifier in Hurthle cell thyroid nodules differs from other indeterminate thyroid nodules. Thyroid. 2015;25(7):789–96.
48. Wharry LI, McCoy KL, Stang MT, Armstrong MJ, LeBeau SO, Tublin ME, et al. Thyroid nodules (≥4 cm): can ultrasound and cytology reliably exclude cancer? World J Surg. 2014;38(3):614–21.
49. Trimboli P, Cremonini N, Ceriani L, Saggiorato E, Guidobaldi L, Romanelli F, et al. Calcitonin measurement in aspiration needle washout fluids has higher sensitivity than cytology in detecting medullary thyroid cancer: a retrospective multicentre study. Clin Endocrinol. 2014;80(1):135–40.
50. Scollo C, Baudin E, Travagli JP, Caillou B, Bellon N, Leboulleux S, et al. Rationale for central and bilateral lymph node dissection in sporadic and hereditary medullary thyroid cancer. J Clin Endocrinol Metab. 2003;88(5):2070–5.
51. Machens A, Dralle H. Biomarker-based risk stratification for previously untreated medullary thyroid cancer. J Clin Endocrinol Metab. 2010;95(6):2655–63.
52. Gharib H, Papini E. Thyroid nodules: clinical importance, assessment, and treatment. Endocrinol Metab Clin N Am. 2007;36(3):707–35, vi.
53. Belfiore A, Russo D, Vigneri R, Filetti S. Graves' disease, thyroid nodules and thyroid cancer. Clin Endocrinol. 2001;55(6):711–8.

54. Guo Z, Yu P, Liu Z, Si Y, Jin M. Total thyroidectomy vs bilateral subtotal thyroidectomy in patients with Graves' diseases: a meta-analysis of randomized clinical trials. Clin Endocrinol. 2013;79(5):739–46.
55. Bahn RS, Burch HS, Cooper DS, Garber JR, Greenlee CM, Klein IL, et al. The role of propylthiouracil in the management of Graves' disease in adults: report of a meeting jointly sponsored by the American Thyroid Association and the Food and Drug Administration. Thyroid. 2009;19(7):673–4.
56. Erbil Y, Ozluk Y, Giris M, Salmaslioglu A, Issever H, Barbaros U, et al. Effect of lugol solution on thyroid gland blood flow and microvessel density in the patients with Graves' disease. J Clin Endocrinol Metab. 2007;92(6):2182–9.
57. Kandil E, Noureldine SI, Abbas A, Tufano RP. The impact of surgical volume on patient outcomes following thyroid surgery. Surgery. 2013;154(6):1346–52; discussion 52–3.
58. Oltmann SC, Brekke AV, Schneider DF, Schaefer SC, Chen H, Sippel RS. Preventing postoperative hypocalcemia in patients with Graves disease: a prospective study. Ann Surg Oncol. 2015;22(3):952–8.
59. Kim WW, Chung SH, Ban EJ, Lee CR, Kang SW, Jeong JJ, et al. Is preoperative vitamin D deficiency a risk factor for postoperative symptomatic hypocalcemia in thyroid cancer patients undergoing total thyroidectomy plus central compartment neck dissection? Thyroid. 2015;25(8):911–8.
60. Gupta A, Ly S, Castroneves LA, Frates MC, Benson CB, Feldman HA, et al. A standardized assessment of thyroid nodules in children confirms higher cancer prevalence than in adults. J Clin Endocrinol Metab. 2013;98(8):3238–45.
61. Monaco SE, Pantanowitz L, Khalbuss WE, Benkovich VA, Ozolek J, Nikiforova MN, et al. Cytomorphological and molecular genetic findings in pediatric thyroid fine-needle aspiration. Cancer Cytopathol. 2012;120(5):342–50.
62. Niedziela M, Breborowicz D, Trejster E, Korman E. Hot nodules in children and adolescents in western Poland from 1996 to 2000: clinical analysis of 31 patients. J Pediatr Endocrinol Metab. 2002;15(6):823–30.
63. Hay ID, Gonzalez-Losada T, Reinalda MS, Honetschlager JA, Richards ML, Thompson GB. Long-term outcome in 215 children and adolescents with papillary thyroid cancer treated during 1940 through 2008. World J Surg. 2010;34(6):1192–202.
64. Sosa JA, Tuggle CT, Wang TS, Thomas DC, Boudourakis L, Rivkees S, et al. Clinical and economic outcomes of thyroid and parathyroid surgery in children. J Clin Endocrinol Metab. 2008;93(8):3058–65.
65. Tuggle CT, Roman SA, Wang TS, Boudourakis L, Thomas DC, Udelsman R, et al. Pediatric endocrine surgery: who is operating on our children? Surgery. 2008;144(6):869–77, discussion 77.
66. Moosa M, Mazzaferri EL. Outcome of differentiated thyroid cancer diagnosed in pregnant women. J Clin Endocrinol Metab. 1997;82(9):2862–6.
67. Kuy S, Roman SA, Desai R, Sosa JA. Outcomes following thyroid and parathyroid surgery in pregnant women. Arch Surg. 2009;144(5):399–406, discussion.
68. Berber E, Bernet V, Fahey TJ, Kebebew E, Shaha A, Stack BC Jr, et al. American Thyroid Association statement on remote-access thyroid surgery. Thyroid. 2016;26(3):331–7.
69. Sun GH, Peress L, Pynnonen MA. Systematic review and meta-analysis of robotic vs conventional thyroidectomy approaches for thyroid disease. Otolaryngol Head Neck Surg. 2014;150(4):520–32.
70. Wang TS, Cheung K, Roman SA, Sosa JA. To supplement or not to supplement: a cost-utility analysis of calcium and vitamin D repletion in patients after thyroidectomy. Ann Surg Oncol. 2011;18(5):1293–9.