Current Problems in Surgery 56 (2019) 103–127

Contents lists available at ScienceDirect

Current Problems in Surgery

journal homepage: www.elsevier.com/locate/cpsurg

Updates in the management of thyroid nodules

Jennifer H. Kuo, MD, MS[a,*], Catherine McManus, MD[a], Claire E. Graves, MD[a], Amin Madani, MD, PhD[a], Mamoona T. Khokhar, MD[b], Bernice Huang, MD[a], James A. Lee, MD[a]

Introduction

Over the past 3 decades, advances in medical technology have drastically improved our ability to detect and diagnose thyroid cancer. The introduction and wide availability of real-time ultrasonography in the 1990s allowed for the detection of smaller thyroid nodules than could be detected by physical examination alone and for more precise fine needle aspiration biopsy (FNAB) which has become the cornerstone for gauging the risk of malignancy in thyroid nodules. The Bethesda system for reporting thyroid cytopathology was introduced in 1997 and stratified malignancy risks across 6 different categories, helping to standardize the management of thyroid nodules. The system quickly gained widespread acceptance and was expanded for use with other malignancies outside of thyroid cancer. However, the success of the Bethesda system in thyroid cancer was limited by 3 indeterminate categories that often led to surgical excision of mostly benign thyroid nodules. This clinical problem fueled the advent of molecular profiling of thyroid cytologic aspirates. This adjunct tool has generally improved our ability to diagnose benign neoplasms within these indeterminate categories, although its utility in predicting malignancy within these indeterminate nodules remains controversial.

However, as the ability to diagnose thyroid cancer in smaller and smaller nodules has increased, the value of doing so has come under increasing scrutiny. Thyroid nodules are extremely common and are detected with high-resolution ultrasound in 19% to 68% of randomly selected individuals. Only a small percentage of these nodules, 7% to 15%, actually represent thyroid cancer. Furthermore, in the early half of this decade, it was noted that the incidence of thyroid

From the [a]Division of Endocrine Surgery, Columbia University, New York, NY; and [b]Division of Endocrine Surgery, Banner University Medical Center, Phoenix, AZ

* Address reprint requests to Jennifer H. Kuo, MD MS, Columbia University, 161 Fort Washington Ave, 8th Floor, New York, NY 10032.

E-mail address: jhk2029@cumc.columbia.edu (J.H. Kuo).

https://doi.org/10.1067/j.cpsurg.2018.12.003

cancer was rising exponentially with approximately 63,000 new cases of thyroid cancer diagnosed in 2014 in the United States compared to 37,200 new cases in 2009 (4.5% per year), without any change in mortality rate. Closer examination of this increased incidence revealed that the rise was mostly in the diagnosis of subcentimeter papillary thyroid cancers ([PTCs] microcarcinomas). In addition, there was mounting evidence that the majority of these microcarcinomas were indolent in nature and had little potential to cause significant morbidity and mortality for patients. In response to increasing concern for the overdiagnosis and treatment of small PTCs, a US Preventative Task Force was commissioned to evaluate the effectiveness and safety of thyroid cancer screening.[1] This Task Force found that although thyroid cancer screening itself was not harmful to patients, it often led to the treatment of small, clinically insignificant microcarcinomas that were associated with a small but not insignificant rate of permanent nerve damage and hypoparathyroidism. In addition, surgical treatment conferred a higher risk that the patient would receive adjuvant radioactive iodine (RAI) ablation which was associated with potential harm to the salivary glands and excess risk of second primary cancers. Finally, although we have made great advances in the *diagnosis* of thyroid cancer from FNABs, we have not made as much advancement in predicting the *behavior* of the thyroid cancer, limiting our ability to differentiate between indolent cancers and more aggressive variants.

Thus, clinicians are now faced with the daunting task of balancing potential harm from overtreatment in the majority of patients with low-risk disease, with appropriate treatment of those patients who are truly at higher risk for disease-specific morbidity and mortality. In this manuscript, we provide an updated review of the available evidence to help clinicians navigate this increasingly complex task.

Thyroid ultrasound

The most widely used imaging modality to evaluate the thyroid is ultrasonography. Not only is ultrasound less expensive and more readily available compared to other radiologic modalities, but the experience with and literature surrounding sonographic evaluation of the thyroid is extensive.[2-6] Patients with a thyroid abnormality on physical examination (such as a suspected nodule or goiter) or with an incidentally discovered nodule on another imaging modality (such as computed tomography [CT], magnetic resonance imaging [MRI] or fluorodeoxyglucose-position emission tomography [FDG-PET]) should undergo evaluation with ultrasound. A dedicated thyroid ultrasound includes characterization of the thyroid parenchyma (homogenous or heterogeneous), size of the isthmus and each lobe (length, width, and height), location and characteristics of thyroid nodules, and evaluation of the central and lateral cervical lymph node compartments.[3] Sonographic evaluation of the thyroid can aid in the diagnosis of many conditions including Graves' disease, thyroiditis, multinodular goiter, and malignancy.

Thyroid nodules

The important characteristics to note for thyroid nodules include echogenicity, presence of calcifications, shape, vascularity, and composition (cystic, solid, or spongiform).[3,4] Studies have demonstrated that certain ultrasound findings correlate with a risk of malignancy which can help guide practitioners in the decision to pursue further evaluation.[5,6] Several characteristics have a high specificity (>90%) for thyroid cancer and include the presence of microcalcifications, a shape that is taller than wide, and irregular margins (spiculated, infiltrative, or microlobulated).[4,7] Additionally, a nodule with an interrupted rim of peripheral calcification is more likely to be malignant (78.9%).[8,9] Although hypoechogenicity may be associated with thyroid cancer, up to 55% of benign nodules are also hypoechoic,[10] demonstrating that although these individual characteristics may have a high specificity, their individual sensitivities are less than 70% to 77%, limiting their utility to predict benign nodules and detect malignant nodules.

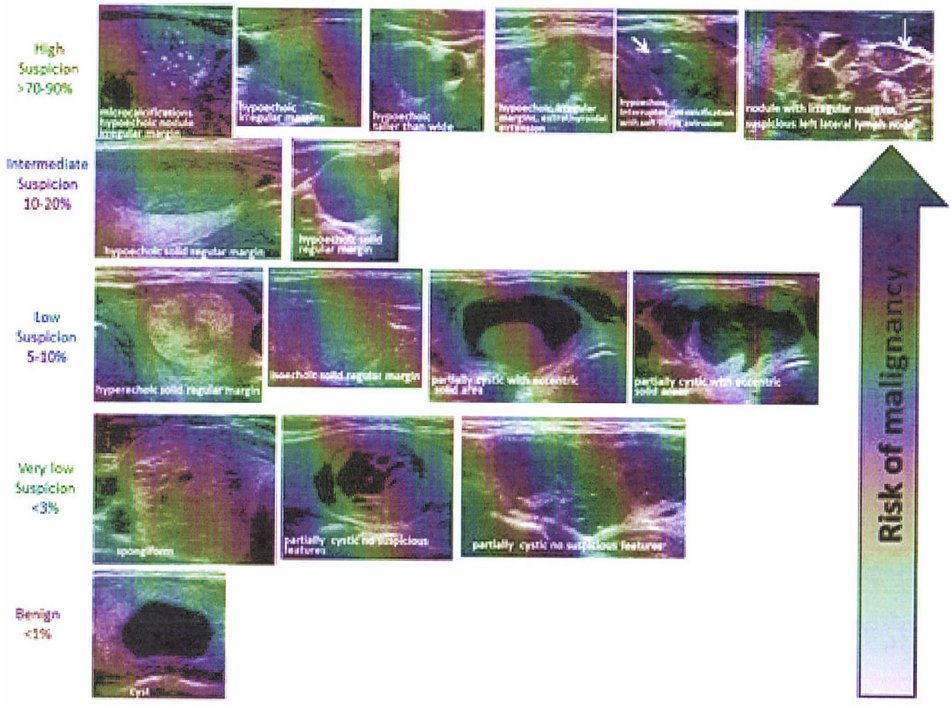

Fig. 1. American Thyroid Association (ATA) ultrasound characteristic patterns and risk of malignancy. Published with permission from Haugen and colleagues.[3]

Most studies evaluating the association of sonographic characteristics of thyroid nodules with malignancy only include patients with papillary thyroid carcinoma (PTC). However, some features on ultrasound are more likely to be found in other types of thyroid cancer. Nodules with follicular thyroid carcinoma (FTC) are more likely to be iso- or hyperechoic, round (width greater than anterioposterior dimension in the transverse view), noncalcified, and have smooth margins.[11] Several studies that include both patients with PTC and FTC demonstrate a correlation of intranodular vascularity with malignancy.[4,6,12] However, a multivariable logistic regression that looked only at patients with PTC demonstrated that intranodular vascularity was not independently predictive of PTC.[13]

Given that no single ultrasound finding is 100% predictive or pathognomonic for thyroid cancer, the American Thyroid Association (ATA) suggests evaluating nodules in terms of a constellation of sonographic features. Using this approach, nodules can be stratified according to the presence of concerning ultrasound characteristics that correspond to a certain risk of malignancy. Clinicians can then determine whether further evaluation with FNAB is warranted.[14-16] The ATA stratifies nodules into 5 groups that correspond to a different risk of malignancy: high suspicion, intermediate suspicion, low suspicion, very low suspicion, and benign (Fig 1, Table 1).

High suspicion

Thyroid nodules in the high suspicion category carry a risk of malignancy ranging from 70% to 90%.[14,15,17] A nodule is considered highly suspicious if it is completely or partially solid and hypoechoic plus has 1 of the following features: irregular margins (microlobulated, spiculated, infiltrative), microcalcifications, a shape that is taller than wide, a disrupted peripheral rim of calcification, or extrathyroidal extension. If a nodule fulfills these criteria and is greater than or equal to 1 cm, an ultrasound-guided FNAB should be performed. If a nodule fulfills these criteria

Table 1
American Thyroid Association (ATA) ultrasound features with estimated risk of malignancy and recommendation for (FNAB), adapted with permission from Haugen and colleagues.[3]

Sonographic pattern	US features	Estimated risk of malignancy, %	FNAB size cutoff (largest dimension)
High suspicion	Solid hypoechoic nodule or solid hypoechoic component of a partially cystic nodule with 1 or more of the following features: irregular margins (infiltrative, microlobulated), microcalcifications, taller than wide shape, rim calcifications with small extrusive soft tissue component, evidence of ETE	>70-90*	Recommend FNAB at ≥1 cm
Intermediate suspicion	Hypoechoic solid nodule with smooth margins without microcalcifications, ETE or taller than wide shape	10-20	Recommend FNA at ≥1 cm
Low suspicion	Isoechoic or hyperechoic solid nodule, or partially cystic nodule with eccentric solid areas, without microcalcifications, ETE, or taller than wide shape	5-10	Recommend FNAB at ≥0.5 cm
Very low suspicion	Spongiform or partially cystic nodules without any of the sonographic features described in low, intermediate, or high suspicion patterns	<3	Consider FNAB at ≥2 cm Observation without FNAB is also a reasonable option
Benign	Purely cystic nodules (no solid component)	<1	No biopsy†

ETE, extrathyroidal extension.
Ultrasound-guided FNA is recommended for cervical lymph nodes that are sonographically suspicious for thyroid cancer.
* The estimate is derived from high volume centers; the overall risk of malignancy may be lower given the interobserver variability in sonography.
† Aspiration of the cyst may be considered for symptomatic or cosmetic drainage.

but is less than 1 cm, has no extrathyroidal extension, no metastatic cervical lymphadenopathy, and no distant metastasis, it may be observed if the patient is older than 60 years of age. Support for this recommendation comes from observational studies of micropapillary thyroid carcinoma, defined as PTC lesions less than 1 cm. Ito and colleagues demonstrated that, compared to patients older than 60 years of age, patients younger than 40 years of age have a higher rate of tumor growth (5.9% vs 2.2% $P < 0.01$) and development of lymphadenopathy (5.3% vs 0.4%, $P < 0.01$).[18] Therefore, when highly suspicious sonographic characteristics are present, there is a lower threshold for FNAB in younger patients even if the nodule measures less than 1 cm.

Intermediate suspicion

Intermediate suspicion nodules carry a malignancy risk of 10% to 20%.[14,15,17] These nodules are hypoechoic, solid, and have a smooth, regular margin with no calcifications, no extrathyroidal extension, and are not taller than wide. Nodules with this appearance have a lower specificity for malignancy compared to the high suspicion group; however, the sensitivity of these sonographic characteristics is 60% to 80%. As a result, if the nodule has these characteristics and is greater than or equal to 1 cm, an FNAB should be done to assess for malignancy.

Low suspicion

Low suspicion nodules have a malignancy risk of 5% to 10%.[14,15,17] These nodules are isoehoic, hyperechoic, or partially cystic with eccentric solid areas and have no calcification or extrathyroidal extension and are not taller than wide. Studies show that 15% to 20% of thyroid cancers

are iso- or hyperechoic and are more commonly FTC.[10] Furthermore, distant metastasis is unlikely if these nodules are smaller than 2 cm.[11] Thus, these nodules can be observed without FNAB unless the size of the nodule is greater than or equal to 1.5-2 cm, in which case an FNAB may be considered.

Very low suspicion

Very low suspicion nodules have a risk of malignancy less than or equal to 3%.[6,14,15,17] These nodules are spongiform or partially cystic and have no calcifications, no extrathyroidal extension, and are not taller than wide. These nodules can be observed. However, FNAB may be considered if the nodule is at least 2 cm.

Benign

Benign nodules, which have a malignancy risk less than 1%, are typically purely cystic nodules. These can be observed unless the patient is symptomatic, in which case they can be aspirated with or without ethanol ablation.[6,14,15,17]

When evaluating a patient with a thyroid nodule, it is important to assign a risk of malignancy to that nodule based on the category of suspicion, but it is also important to factor in patient risk factors. If the patient has risk factors that are associated with thyroid cancer including symptoms (pain, dysphagia, cough, and hoarseness), a growing thyroid nodule, a history of radiation exposure as a child, or familial cancer, FNAB should be considered at lower size cutoffs for all risk categories.[19]

Another cancer risk stratification system for thyroid nodules based on ultrasound findings was developed by the American College of Radiology and published as the Thyroid Imaging, Reporting Data System (TI-RADS).[2] TI-RADS organizes nodules into 5 classifications (benign, minimally suspicious, moderately suspicious, or highly suspicious for malignancy) based on points assigned from 5 different sonographic categories. The practitioner selects 1 feature from each of the first 4 categories (composition, echogenicity, shape, and margins) and all of the features that apply in the fifth category (echogenic foci) and sums the points to determine the classification (Fig 2). Based on the assigned classification, the TI-RADS score will recommend whether or not an FNAB is indicated.[20] Similar to the ATA guidelines, TI-RADS risk can help quantify the risk of malignancy in thyroid nodules based on suspicious sonographic findings. Single and multi-institution studies have individually validated both the ATA and ACR TI-RADS systems and demonstrated that either system can reliably be used for risk stratification of thyroid nodules.[21-24] Furthermore, studies have shown that by using either the ATA or ACR TI-RADS systems, unnecessary FNAB can be avoided without missing clinically significant thyroid cancer.[24-26]

Lymph nodes

In addition to evaluating thyroid nodules, the sonographer must evaluate the central and lateral cervical lymph node compartments in all patients being evaluated for thyroid disease. Studies have demonstrated that even if a nodule is small, up to 20% to 50% of differentiated thyroid cancers have metastases to cervical lymph nodes and micrometastases (<2 mm) may be present in up to 90% of patients.[27-34] Preoperative sonographic evaluation of the lymph nodes identifies up to 20% to 30% of suspicious cervical adenopathy, which may lead to a change in management, including FNAB of a nodule or suspicious lymph node, in up to 20% of patients.[35-39] It is important to keep in mind that ultrasound may only identify one-half of the lymph nodes that are suspicious for malignancy that are discovered at the time of the operation.[40]

Similar to thyroid nodules, cervical lymph nodes also have certain sonographic features that should raise concern for malignancy. These characteristics include enlargement, loss of the fatty hilum, a rounded rather than oval shape, calcifications, hyperechogenicity, cystic change, and peripheral vascularity (Table 2). One study demonstrated that loss of the fatty hilum was the most sensitive finding for malignancy at 100%; however, the specificity was low, at only

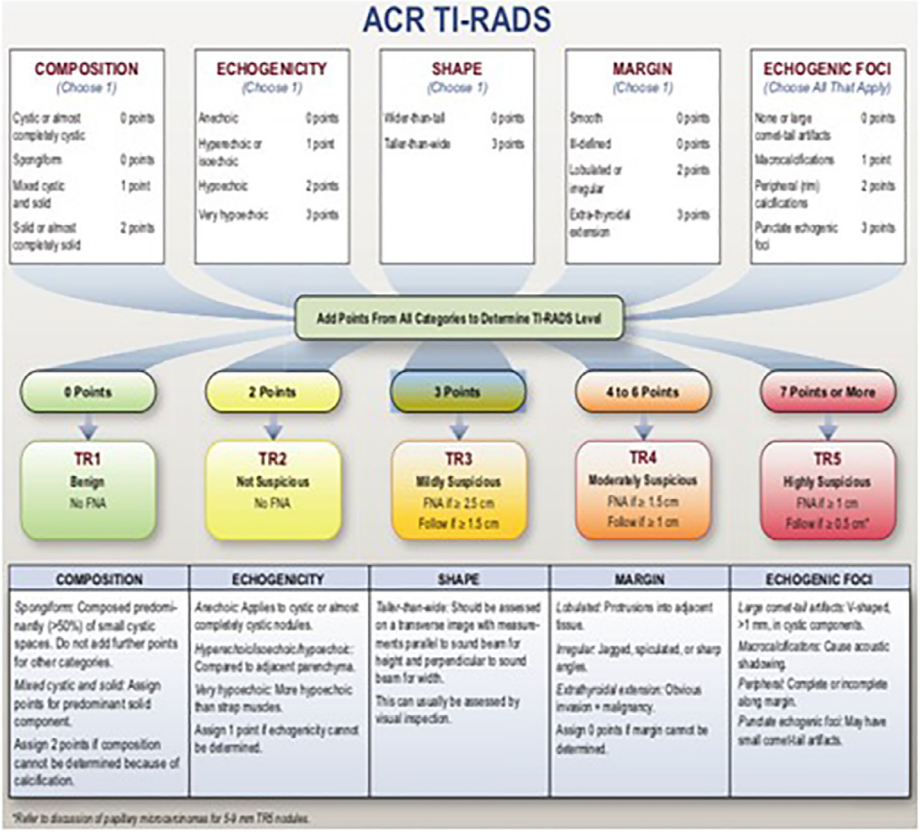

Fig. 2. American College of Radiology (ACR) Thyroid Imaging, Reporting and Data System (TI-RADS). Published with permission from Tessler and colleagues.[20]

Table 2
Sonographic characteristics of lymph nodes with corresponding sensitivity and specificity.[150,151]

Sonographic feature	Reported sensitivity, %	Reported specificity, %
Loss of fatty hilum	83-100	48-56
Cystic change	10-34	91-100
Peripheral vascularity	10-86	57-93
Hyperechogenicity	30-87	43-95
Round shape	37-55	70-89

29%.[41,42] Another study showed that peripheral vascularity was the most sensitive (86%) but only carried a specificity of 82%. The most specific characteristics included a short axis (>5 mm; 96%), presence of cystic areas (100%), hyperechogenicity (100%), and microcalcifications (100%).[40] If a lymph node has any of these characteristics and is 8 mm or larger, the patient should undergo FNAB.

In summary, thyroid ultrasound is the recommended initial radiographic study of choice to evaluate for thyroid pathology. A wealth of literature supports using sonographic characteristics of both thyroid nodules and cervical lymph nodes in risk stratifying and determining the need for FNAB. Utilizing validated common scoring systems like those produced by the ATA and ACR

is critical not only in deciding when a FNAB is indicated but also in improving communication and continuity of care for patients among health care providers.

Cytopathology and the Bethesda classification system

FNAB is an important diagnostic tool in the evaluation of thyroid nodules. To improve communication between clinicians and to facilitate research, the Bethesda system for reporting thyroid cytopathology was first developed in 2009 to serve as a standardized framework for reporting thyroid FNAB results.[43] The Bethesda system has been widely adopted and, recently revised in 2017,[44] remains the cornerstone of thyroid cytopathologic diagnosis.

The Bethesda system recommends that each report begin with 1 of 6 diagnostic categories: (1) nondiagnostic/unsatisfactory, (2) benign, (3) atypia of undetermined significance/follicular lesion of undetermined significance, (4) follicular neoplasm/suspicious for a follicular neoplasm, (5) suspicious for malignancy, or (6) malignant (Table 3). Each category confers a risk of malignancy and is linked to evidence-based guidelines for clinical management. The 2017 revisions retained the original 6 diagnostic categories, but updated the risk of malignancy of each category to reflect more recent data. Importantly, the revisions also included the reclassification of noninvasive follicular variant of PTC, a subset of PTC that behaves similarly to follicular adenoma, to noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP). This change in terminology better conveys the characteristics and prognosis of this variant with the intent of avoiding overtreatment.[45] Thus, in the revised Bethesda system, the risk of malignancy for each diagnostic category was recalculated in 2 ways: including NIFTP among malignancies, and excluding it from malignancies. The new system also accounts for the advent of molecular testing and its role in further refining the estimate of malignancy of indeterminate thyroid nodules.

Nondiagnostic or unsatisfactory (Bethesda I)

All specimens from thyroid FNAB should first be evaluated for sample adequacy. A specimen is considered adequate when there is significant atypia identified or when a specific diagnosis can be made. In order to satisfactorily determine that a specimen is benign, it must contain at least 6 groups of benign follicular cells, each having at least 10 cells. Specimens that contain abundant colloid are excluded from this requirement, as this is characteristic of a predominately macrofollicular benign nodule. The rate of malignancy in nondiagnostic nodules is estimated to be approximately 5%-10%. Repeat ultrasound-guided FNAB is recommended for nondiagnostic nodules, and excision considered for those that remain nondiagnostic after repeat FNA. Management of nondiagnostic specimens containing cyst contents only depends on correlation with ultrasound findings. These nodules may be managed as benign nodules if there are no worrisome sonographic features.

Benign (Bethesda II)

Approximately 60-70% of thyroid FNAs are classified as benign with a very low false-negative rate (<3%), allowing patients with cytologically benign nodules to avoid unnecessary surgery. Ultrasound-guided FNAB with visualization of needle placement within the nodule decreases the false-negative rate of benign cytology.[46] Benign specimens may be subclassified based on a variety of descriptive diagnoses. The most common of these is “consistent with a benign follicular nodule,” which correlates to nodules of a multinodular goiter or follicular adenomas. Benign nodules require no further immediate diagnostic studies or treatment, and are managed with clinical and ultrasound follow-up.[3] Although no standardized interval has been determined, large-scale studies indicate that repeat follow-up at 2-3 years may be cost-effective and safe.[47,48]

Table 3
The 2017 Bethesda system for reporting thyroid cytopathology.

	Diagnostic category	Risk of malignancy (%)		Management
		NIFTP excluded from malignancies	NIFTP included as malignancy	
I	Nondiagnostic or unsatisfactory Cyst fluid only Virtually acellular specimen Other (obscuring blood, etc.)	5-10	5-10	Repeat FNAB with US guidance
II	Benign Consistent with benign follicular nodule Consistent with lymphocytic (Hashimoto) thyroiditis in clinical context Consistent with granulomatous (subacute) thyroiditis Other	0-3	0-3	Clinical and sonographic follow-up
III	Atypia of undetermined significance or Follicular lesion of undetermined significance	6-18	~10-30	Repeat FNAB, molecular testing, or lobectomy
IV	Follicular neoplasm or suspicious for a follicular neoplasm Specify if Hürthle cell type	10-40	25-40	Molecular testing, lobectomy
V	Suspicious for malignancy Suspicious for papillary carcinoma Suspicious for medullary carcinoma Suspicious for metastatic carcinoma Suspicious for lymphoma Other	45-60	50-75	Near-total thyroidectomy or lobectomy
VI	Malignant Papillary thyroid carcinoma Poorly differentiated carcinoma Medullary thyroid carcinoma Undifferentiated (anaplastic) carcinoma Squamous cell carcinoma Carcinoma with mixed features Metastatic carcinoma Non-Hodgkin lymphoma Other	95-96	97-99	Near-total thyroidectomy or lobectomy

Table adapted from Cibas ES and Ali SZ.[44]
FNAB, fine needle aspiration biopsy; NIFTP, noninvasive follicular thyroid neoplasm with papillary-like nuclear factors.

Atypia or follicular lesion of undetermined significance (Bethesda III)

Bethesda III lesions are the most heterogeneous. This is generally considered a category of last resort for FNAs not easily classified elsewhere and should account for no more than 10% of specimens. Although a laboratory can choose either name, only 1 should be used consistently for all specimens in this category. “Atypia of Undetermined Significance” (AUS) is the broader term of the 2, as “Follicular Lesions of Undetermined Significance” (FLUS) specifies follicular origin. Descriptions are encouraged to subclassify the type of atypia, if possible. The risk of malignancy in this category has been difficult to define, as only a small number of nodules are excised - generally for suspicious features clinically or on ultrasound, or abnormal results on molecular testing or repeat FNAB. Therefore, the excised subset overestimates the risk of malignancy. This category includes a significant proportion of NIFTP, and estimates suggest that the reclassification lowers the risk of malignancy by up to 59%.[49] When NIFTP is included as a malignancy, the risk is estimated at 10%-30%, but drops to 6%-18% after exclusion. Due to the heterogeneity

of this classification, management of these nodules must include consideration of clinical and radiographic features, and usually includes molecular testing. Repeat FNAB or lobectomy should also be considered.

Follicular neoplasm or suspicious for a follicular neoplasm (Bethesda IV)

As with Bethesda III lesions, either follicular neoplasm (FN) or suspicious for follicular neoplasm (S-FN) may be used for this category, but only 1 name should be used consistently by each laboratory and the 2 terms should not designate different diagnostic categories. Although FNAB is not diagnostic for follicular carcinoma, there are cytomorphologic features that distinguish them from benign follicular neoplasms, such as disordered cytoarchitecture in microfollicular or trabecular arrangements. Although specimens that demonstrate nuclear features of papillary carcinoma were initially excluded from this category in the 2009 guidelines, the 2017 update modified this exclusion in light of NIFTP to include "mild nuclear changes" without other clear characteristics of PTC.[44] These nuclear changes suggest the possibility of follicular variant of PTC or NIFTP and should be delineated in a description included with the diagnosis.

The risk of cancer when NIFTP is included as a malignancy is estimated at 25%-40% in this category, and when NIFTP is excluded, the risk is 10%-40%. Most specimens in this category are ultimately found to be follicular adenomas or adenomatoid nodules of multinodular goiter, rather than follicular carcinoma. Molecular testing may be used for specimens in this category to augment the risk assessment, but excision is typically recommended.

Suspicious for malignancy (Bethesda V)

Although many thyroid cancers can be diagnosed with certainty by FNAB, some may be incompletely sampled and others may have more subtle morphology, making them difficult to differentiate from benign lesions. The Bethesda V category encompasses specimens that have only 1 or 2 characteristic features of malignancy, features that are focal rather than widespread throughout the specimen, and/or specimens that are less cellular. This diagnosis is used most commonly when the specimen is suspicious for PTC and includes a significant proportion of specimens reclassified as NIFTP.[49,50] Therefore, the risk of malignancy drops from 50% to 75% when NIFTP is included in the malignant category to 45% to 60% when it is considered benign. To confirm the diagnosis, and because of the risk of malignancy is high, surgical resection is indicated.

Malignant (Bethesda VI)

This category is used when cytologic features are conclusive for malignancy. Further description may subclassify the malignancy. When NIFTP is included as a malignancy, the risk of cancer in this category is 97% to 99%. When NIFTP is not considered a malignancy, the risk decreases to 94% to 96%. With the exception of some widely metastatic tumors, surgical resection is indicated for these lesions.

Molecular profiling of indeterminate thyroid nodules

Objectives of molecular testing

Despite the diagnostic utility, low cost, and widespread use of sonographic and cytopathologic assessments of thyroid nodules to assist with the risk stratification for malignancy,

10% to 40%[51-53] of nodules will be classified as indeterminate (Bethesda III, IV, or V) with a risk of malignancy ranging from 5% to 85%.[54-56] Ultimately, 60% end up being resected, and the large majority (85% of AUS-FLUS, 75% of FN-SFN, and 35% of SM) are benign, underscoring the need for a more precise means of assessment in order to minimize surgical overtreatment.[54,57] Growing knowledge of thyroid tumor biology and molecular genomics over the last 2 decades has led to advancements in molecular profiling. As a result, a variety of diagnostic tools have become available to complement cytology and improve our ability to distinguish nodules that warrant surgery from those that can be safely observed.

Types of molecular tests

Molecular profiling can be divided broadly into 2 general approaches.[58] A "rule-out" approach includes diagnostic tests that demonstrate a high sensitivity and negative predictive value (NPV), similar to a cytopathologic benign diagnosis. These tests can rule out malignancy with a high degree of reliability. Conversely, a "rule-in" approach has a high specificity and positive predictive value (PPV), similar to a cytopathologic malignant diagnosis, and would be most useful in situations where a high preoperative probability of malignancy would change the surgical management from a diagnostic lobectomy (and a potential second-stage completion thyroidectomy) to a single-stage total thyroidectomy. These tests should be used judiciously given that lobectomy is now considered an acceptable option for PTCs up to 4 cm in size, with no extrathryoidal extension, cervical lymph nodes, distant metastases, or history of radiation exposure, according to the most recent National Comprehensive Cancer Network and ATA guidelines.[3]

Gene expression classifiers

Gene expression classifiers (GECs) quantify the mRNA expression of multiple candidate genes within the entire transcriptome of the sample tissue. A proprietary algorithm using advanced statistical modelling and machine learning subsequently stratifies the pattern of mRNA gene expression into 1 of 2 molecular signatures: benign or suspicious.[59,60] The most studied GEC test is the Afirma Gene Classifier (Veracyte Inc., San Francisco, CA), whereby additional FNA samples are obtained, stored and shipped to a designated outside laboratory using specialized RNA-preserving tubing and solution. The tissue is analyzed for 167 genes after an initial exclusion of various rare neoplasms (such as medullary thyroid cancer, parathyroid neoplasms, melanoma, breast cancer, and renal cell carcinoma). The diagnostic utility of this approach was initially demonstrated in 2 prospective studies.[59,61] In a large multicenter trial, Alexander and colleagues analyzed 265 indeterminate thyroid nodules larger than 1 cm with independent blinded surgical pathologic confirmation, and reported an overall NPV of 93% (including 95% for AUS-FLUS, 94% for FN-SFN, and 85% for SM), and overall sensitivity of 92% (including 90% for AUS-FLUS, 90% for FN-SFN, and 94% for SM).[61] Based on these results, many have suggested that the Afirma GEC test be used as a "rule-out" test for AUS-FLUS and FN-SFN nodules, given that the likelihood of finding a malignancy with a "benign" GEC result is comparable to that of a nodule with a benign Bethesda II cytology result (5%). However, given its very low specificity (52%), it remains inadequate as a confirmatory test to rule in malignancy. Since these initial studies, there have been numerous subsequent independent validation studies that have attempted to replicate these results. Despite various limitations in methodology, the PPV in "suspicious for malignancy" samples was significantly lower, and the NPV seems to decrease to less than 90% in centers with a higher prevalence of malignancy,[62-64] thus bringing into question the reproducibility of the test's performance. Similarly, a multicenter follow-up study by Alexander and colleagues demonstrated large interinstitutional variations in the prevalence of malignancies confirmed by surgical pathology (33%-80% for AUS-FLUS and 33%-67% for FN-SFN), despite not reaching statistical significance.[65] Given the strong correlation of NPV with the prevalence of malignancy in the study population, it has been suggested that a pretest risk of malignancy of less than 23% is required for the NPV to be greater than 95% (i.e., equivalent to a benign cytology result).[66] Nonetheless, long-term data on Afirma GEC's impact on clinical decision-making has shown a

significant reduction in rates of diagnostic lobectomies for indeterminate nodules with a benign Afirma GEC result compared to historical controls.[67,68]

Recently, the newer Afirma Genomic Sequencing Classifier (GSC) has been introduced in an effort to improve its diagnostic yield. The GSC uses next-generation sequencing (NGS) technology to provide more robust methods to sequence nucleic acids and quantify RNA expression in the context of 1115 core genes.[69] In addition, the test also runs the sample through various classifiers ("cassettes") designed to improve its accuracy, including a follicular content index, Hürthle cell index, and Hürthle cell neoplasm index. Using 183 FNAB indeterminate samples from the initial prospective blinded multicenter study that validated Afirma GEC,[61] Patel and colleagues similarly compared the diagnostic accuracy of Afirma GSC.[69] They were able to demonstrate, in a population with a 24% prevalence of malignancy, a sensitivity of 91% (AUS-FLUS: 93%; FN-SFN: 88%), specificity of 68% (AUS-FLUS: 71%; FN-SFN: 64%), NPV of 96% (AUS-FLUS: 97%; FN-SFN: 95%), and PPV of 47% (AUS-FLUS: 51%; FN-SFN: 42%). Furthermore, the NPV remained greater than 95% despite variations in cancer prevalence from 10% to 30%, which is the rate expected for Bethesda III and IV lesions.[56] This improvement in performance suggests that the test would maintain its utility as a "rule-out" test (even in populations with a greater risk of malignancy), while further minimizing the number of patients undergoing unnecessary diagnostic lobectomy.

Mutation panels

The identification of cancer-specific DNA mutations can also be used for molecular profiling. This was initially done using a 7-gene panel consisting of BRAF, NRAS, HRAS, KRAS, PTC1 (gene fusion of RET and CCDC6), PTC3 (gene fusion of RET and NCOA4), and PAX8-PPAR-gamma gene fusions, which detected 60% of malignancies among indeterminate nodules.[70] Other known mutations include TP53 and CTNNB1 in poorly differentiated and anaplastic cancers, and the RET gene in medullary thyroid cancers.[71-73] Unfortunately, the 7-gene panel showed low sensitivity and NPV, and highly variable PPV and specificity in prospective studies.[74-76] Since then, it has been modified into the ThyGenX (PDI Inc., Parsippany, NJ), which uses targeted NGS to detect mutations across the same 7-gene panel in addition to PIK3CA, often seen in follicular and anaplastic cancers,[77,78] or its newer model, ThyGeNEXT, which incorporates the detection of more than 150 genetic alterations linked to differentiated thyroid cancers.[76] Currently, ThyGenX and ThyGeNEXT tests are offered in conjunction with ThyraMIR, a microRNA classifier test.

After the Thyroid Cancer Genome Atlas comprehensively described the genetic background and oncogenic driver of a sample of 496 PTCs, Nikiforov and his team expanded the 7-gene panel test to include newer mutations (including 12 genes and 42 gene fusions) as part of a targeted NGS methodology in an effort to improve sensitivity and NPV.[76,79,80] This eventually expanded into ThyroSeq v2 (CBLPath Inc., Rye Brook, NY), which detects mutations in AKT1, BRAF, CTNNB1, GNAS, HRAS, KRAS, NRAS, PIK3CA, PTEN, RET, TP53, TSHR, TERT, and EIF1AX, and 42 gene rearrangements, including in RET, PPAR-gamma, NTRK1, NTRK3, BRAF, and ALK.[81] Nikiforov and colleagues evaluated the performance of ThyroSeq v2 on 143 FN-SFN FNA samples with known histopathology and demonstrated a 90% sensitivity, 93% specificity, 96% NPV, and 83% PPV.[81] Using a pretest probability of malignancy between 14% and 34%, the NPV and PPV were modelled at 95% to 98% and 68% to 87% respectively, making the ThyroSeq v2 useful both as a "rule-out" and "rule-in test". These data were further extrapolated to AUS-FLUS cytology using a pretest probability of malignancy of 5% to 15%, which demonstrated a NPV of 98% to 99% and a PPV of only 40%-69%. This sharp decrease in PPV is likely a result of the comprehensive mutation assessment, which increases the rate of false-positives, making it unsuitable as a "rule-in" test in populations with a lower prevalence of malignancy. In addition, there have been no prospective studies with independent blinded histopathologic assessments of indeterminate FNAB samples. More recently, the latest version of this test, ThyroSeq v3, detects 112 genes (including the ones that were incorporated into ThyroSeq v2). Using an initial group of surgically removed specimens as a training set, and a subsequent group of FNAB samples with histopathologic confirma-

tion as a validation set, the same team was able to demonstrate a 98% sensitivity, 82% specificity, and 91% accuracy.[82] Specifically for lesions with Hürthle cells, whose malignant potential are often difficult to predict using cytopathology, the test had a 93% sensitivity and 69% specificity.

RAS mutation and noninvasive follicular tumors with papillary-like nuclear features (NIFT-P)

After the BRAF V600E mutation, which is highly specific for PTC (>99%),[83] RAS mutations (including HRAS, NRAS, and KRAS) are the second most common mutations detected in thyroid cancers, especially follicular types. Nevertheless, they are not specific for malignancy since as many as 30% of follicular adenomas harbor such a mutation,[84] thereby bringing into question its utility as a diagnostic tool. In a case series of FNAB samples from thyroid nodules prospectively analyzed by Gupta and colleagues, the majority of RAS-positive samples (93%) were indeterminate on cytology.[85] Furthermore, after histopathologic confirmation, the majority of these samples were designated as follicular variant of PTC (fvPTC), with most of these showing no signs of vascular/capsular invasion or infiltrative growth—consistent with the newer nomenclature of NIFTP. In a similar group of RAS-positive patients, Patel and colleagues have shown that 24% were follicular adenomas, while 76% were malignant (83% of which were consistent with fvPTC).[86] The risk of cancer was 92% (HRAS), 74% (NRAS), and 64% (KRAS) depending on the specific mutation isoform. Since the new designation of NIFTP for tumors initially labelled as encapsulated fvPTC, a study by Paulson and colleagues showed that 60% of RAS-positive thyroid cancers are NIFTP.[87] This suggests that patients with RAS-positive indeterminate nodules should initially be offered a lobectomy as opposed to a thyroidectomy.

Incorporation of microRNA classifiers with mutation panels

MicroRNAs are small noncoding RNAs, whose expression is dysregulated in thyroid cancers and reflects changes in the expression of various oncogenes and tumor-suppression genes. What makes this test so promising is its relative molecular stability during handling and processing of the sample, as well as its histologic-specific and cancer-specific expression profiles. To date, various microRNA classifiers have been derived, demonstrating high specificity and sensitivity,[88] and have recently been combined with DNA mutation panel tests as part of a 2-step approach to help improve diagnostic accuracy. This combination has shown promise in differentiating between RAS-positive benign and malignant follicular lesions.[89-91] More recently, ThyGenX and its newer version ThyGeNEXT were combined with a microRNA classifier (ThyraMIR) into a 2-step methodology (Interpace Diagnostics LLC, PDI Inc., Parsippany, NJ). In this approach, mutation-positive samples are initially screened as “positive” without a second microRNA test (due to the high PPV of ThyGenX), whereas mutation-negative samples are further subjected to a second round of ThyraMIR testing (due to the low sensitivity of ThyGenX). A blinded multicenter cross-sectional study evaluated 109 of Bethesda III and IV lesions using the 7-gene mutation panel followed by a microRNA classifier based on the expression of 10 microRNA genes.[92] This algorithm yielded a sensitivity and specificity of 89% and 85%, respectively. With a malignancy prevalence of 32%, the algorithm had a NPV of 94% and PPV of 74%. Similar to Afirma GEC, Afirma GSC, and ThyroSeq v2, the diagnostic performance varies according to the prevalence of thyroid cancer, where a pretest probability of cancer of at least 20% is required to maintain a PPV greater than 60%.

Rosetta GX Reveal (Rosetta Genomics Ltd, Rehovot, Israel) is another assay classifier test that profiles 24 microRNAs and can be performed using material from regular FNA smears without requiring a dedicated fresh sample.[93] After the classifier was developed according to the expression profile of a sample of 375 Bethesda II-VI thyroid nodules, Lithwick-Yanai and colleagues evaluated the test’s performance in a retrospective multicenter blinded study of 189 samples. Among AUS-FLUS and FN-SFN nodules, the test had a sensitivity greater than 95% but a

specificity of only 80%, and while the NPV remained high for a malignancy prevalence of 20% to 30%, the PPV ranged from 55% to 65%. Although Rosetta GX Reveal had similar performance characteristics as the other available commercial tests, it never gained widespread use and is currently not available on the market.

Impact on clinical practice and decision-making

It is critical to use molecular profiling methodologies judiciously and cost effectively, reserving their use for situations where the results would alter the management of the patient. In order to do so, the clinician must make a comprehensive assessment of the pretest probability of malignancy based on clinical risk factors (such as history of radiation exposure or strong family history of thyroid cancer), both sonographic and cytopathologic features of the nodules in question, as well as the prevalence of thyroid cancer in their local population.[3] What is clear from the numerous validation studies done for the myriad molecular tests is that the utility of these assays varies significantly depending on the prevalence of thyroid cancer for various subgroups. Therefore, patient management can be tailored to the appropriate context either by using an appropriate "rule-in" or "rule-out" test. For instance, molecular testing is not indicated if a lesion exhibits high-risk features (e.g., Bethesda V and VI cytology, history of radiation exposure, microcalcifications on ultrasound). Furthermore, despite the high NPV for most of these tests, in a practice with a 50% risk of malignancy in the population, the NPV would drop to less than 90%, making it suboptimal as a "rule-out" test. On the other hand, for most practices that have malignancy rates less than 30%, most of the tests discussed in this review have NPVs near 95% or greater, and the choice of test ultimately rests on other factors, such as insurance coverage, costs, shipping to extra-institutional laboratories, and ease of obtaining samples (e.g., extra FNAB passes). Finally, most tests have PPVs that are less than ideal for ruling-in malignancy, and given that lobectomy is increasingly considered adequate for many thyroid cancers, such tests would change the surgical management from a diagnostic lobectomy to a total thyroidectomy in only a small proportion of patients with indeterminate nodules,[3] thereby limiting their utility as a "rule-in" test. The tests described in this section are summarized in Table 4.

Follow-up and surveillance of benign thyroid nodules

Given that the majority of thyroid nodules are benign, it is imperative that clinicians use evidence-based approaches, such as the ATA guidelines, for their evaluation, management, and follow-up.

Follow-up of nodules that do not meet FNA criteria

Ultrasound may find nodules that do not meet criteria for FNAB at the time of detection. The majority of thyroid nodules are subcentimeter in size, where FNAB evaluation is generally not indicated. Many nodules larger than a centimeter may also be followed without FNAB, as dictated by the sonographic patterns and size cutoffs outlined in guidelines like the 2015 ATA Thyroid Nodule Guidelines.[3]

The correlation between sonographic features and malignancy risk can be used to guide the follow-up strategy for nodules that do not meet FNAB criteria at the time of initial imaging. Studies indicate that subcentimeter nodules with very low-risk sonographic features have an extremely low risk of malignancy, and are highly unlikely to change during ultrasound follow-up.[94] Nodules with high-risk sonographic patterns, in comparison, carry an estimated risk of malignancy of greater than 70%-90%.[3] It follows that surveillance ultrasonography for a nodule with high-risk sonographic features, with its greater risk of malignancy, should be at a shorter interval than for a nodule with a very low-risk sonographic pattern. The follow-up of nodules

Table 4
Summary of available molecular diagnostic tests for indeterminate nodules.

Test	Mechanism	Cost	Advantages	Disadvantages
Afirma GEC	- Quantifies downstream mRNA gene expression	$4875	- High NPV (>90%) - High sensitivity (>90%) - Evidence to demonstrate significant decrease in diagnostic lobectomy for indeterminate nodules	- Requires repeat FNAB sample shipped in specialized tubing - NPV decreases in populations with higher prevalence of malignancy (risk of malignancy >23%)
Afirma GSC	- More robust mRNA expression and bioinformatics modelling	$6400	- High NPV (>95%), despite variations in prevalence of malignancy - High sensitivity (>90%) - Higher specificity and PPV than Afirma GEC	- Requires repeat FNAB sample shipped in specialized tubing
ThyroSeq v2/v3	- DNA mutation panel	$3200	- High NPV (>95%) - Variable PPV (40-85%) - Only requires a single pass FNAB	- Lack of data to demonstrate clinical effectiveness
ThyGenX	- DNA mutation panel	$1675	- High but variable PPV and specificity - Improved performance when combined with ThyraMIR - Requires only one FNA pass	- Requires shipping in specialized tubing
ThyraMIR	- Assay for microRNA expression profile - Available in combination with ThyGenX	$3300 (ThyGenX + ThyraMIR)	- High NPV (>95%) and modest PPV with combined with ThyGenX	- Requires shipping in specialized tubing
Rosetta GX Reveal	- Assay for microRNA expression profile	N/A	- Does not require repeat smear - High NPV (>90%) - Modest sensitivity (<90%)	- Currently unavailable on the market

Costs are depicted in US dollars.
FNAB, fine-needle aspiration biopsy; GEC, gene expression classifier; GSC, genomic sequencing classifier; NPV, negative predictive value; PPV, positive predictive value.

that do not meet FNAB criteria is therefore based on their sonographic pattern (Table 5):[3] Nodules with high-risk sonographic features should have a repeat ultrasound in 6-12 months. For nodules with low to intermediate risk sonographic patterns, a repeat ultrasound should be considered at 12-24 months. For nodules larger than 1 cm that have very low-risk sonographic features or are pure cysts, the utility and timing of surveillance ultrasonography is not known. If ultrasound is repeated, it should be done at or after 24 months. Nodules less than or equal to 1 cm that have very low suspicion sonographic patterns or are pure cysts do not require routine sonographic follow-up. Ultrasound-guided FNAB should be performed on follow-up if the nodule then meets the FNAB criteria outlined by the 2015 ATA Thyroid Nodule Guidelines.[3]

Table 5
2015 ATA Thyroid Nodule Guidelines: follow-up of nodules that do not meet FNAB criteria.[32]

Sonographic pattern	Follow-up recommendation	Strength of recommendation	Quality of evidence
High suspicion	Repeat ultrasound in 6-12 months	Weak	Low
Low to intermediate suspicion	Consider repeat ultrasound at 12-24 months	Weak	Low
Very low suspicion or pure cysts that are >1 cm	If ultrasound repeated, repeat at or after 24 months	No recommendation	Insufficient evidence
Very low suspicion or pure cysts that are ≤1 cm	Routine sonographic follow-up not required	Weak	Low

Table 6
2015 ATA Thyroid Nodule Guidelines: follow-up of nodules with benign FNAB cytology.[32]

Sonographic pattern	Follow-up recommendation	Strength of recommendation	Quality of evidence
High suspicion	Repeat ultrasound and ultrasound-guided FNAB within 12 months	Strong	Moderate
Low to intermediate suspicion	Repeat ultrasound within 12-24 months; if development of suspicious sonographic features or growth, could repeat FNAB (or continue observation)	Weak	Low
Very low suspicion	If ultrasound repeated, repeat at or after 24 months	Weak	Low
Nodule that has undergone repeat ultrasound-guided FNAB with second benign result	Continued surveillance with ultrasonography no longer indicated	Strong	Moderate

Follow-up of nodules with benign FNA cytology

Ultrasound-guided FNAB of thyroid nodules has a low false-negative rate. A 5-year prospective multicenter study evaluating outcomes for 1597 sonographically or cytologically benign nodules reported a false-negative rate of 1.1% for nodules with benign FNA cytology.[94] Repeat ultrasound-guided FNAB of nodules with initial benign cytology show a higher detection rate of missed malignancies in nodules with high-risk sonographic features rather than in nodules that display growth.[95,96] Kwak and colleagues and Rosario and colleagues both demonstrated a higher malignancy rate in nodules with initial benign cytology that exhibited high-risk sonographic patterns (17.4%-20.4%) vs those that grew but did not exhibit high-risk sonographic features (1.3%-1.4%). The follow-up of thyroid nodules with benign FNAB cytology is therefore based on sonographic pattern (Table 6):[3]

Nodules with high-risk sonographic features should have a repeat ultrasound and ultrasound-guided FNA within 12 months. For nodules with low to intermediate risk sonographic patterns, a repeat ultrasound should be performed within 12-24 months. If there is development of suspicious sonographic features (e.g., irregular margins, microcalcifications, taller than wide), an FNAB could be repeated.

Additionally, if there is growth in the nodule, defined as a 20% increase in at least 2 nodule dimensions (with a minimal increase of more than 2 mm) or more than 50% increase in volume, an FNAB could be repeated. Alternatively, observation could be continued with a repeat ultrasound and a second FNAB if there is persistent growth. For a nodule with very low suspicion sonographic features, the utility of surveillance ultrasonography and use of nodule growth as an

indication for repeat FNAB to detect missed malignancy is limited. It is therefore recommended that, if ultrasound is repeated, it should be done at or after 24 months.

The risk of malignancy after 2 benign FNAB results is virtually zero.[95,97-101] If a nodule has undergone a repeat ultrasound-guided FNA with a second benign result, continued surveillance with ultrasonography is no longer indicated (Table 5).

Follow-up of nodules with indeterminate FNA cytology molecularly profiled as benign

Bethesda III and IV lesions carry an estimated risk of malignancy of 5% to 15% and 15% to 30%, respectively.[44] Molecular marker testing may be used to refine the risk assessment in these nodules, in lieu of proceeding directly to repeat FNAB or diagnostic surgery. In a prospective study of 653 nodules with AUS/FLUS cytology from a single institution, 94% of nodules with a negative mutation analysis were benign on final pathology.[74] A multi-institutional study using GEC for AUS/FLUS nodules found a NPV of 95%. For nodules with a FN/SFN cytology, GEC testing was similarly reported to have a NPV of 94%.[61] Nodules that are cytologically classified as Bethesda III or IV that are benign on GEC have an estimated risk of malignancy that approaches 5% to 6%.[61,74] After consideration of clinical and sonographic features, an indeterminate nodule that has been molecularly profiled as benign may therefore be followed. The presence of high suspicion sonographic features does, however, confer a higher risk of malignancy in indeterminate nodules.[102-105]

Surgical management of small thyroid cancers

Tumor size has long been considered an important prognostic factor in DTC.[106,107] Clinicians generally agree that DTC that are larger than 4 cm diameter or high risk should be treated with total thyroidectomy.[3,108] For low-risk nodules smaller than 1 cm diameter, recent guidelines have shifted toward surveillance rather than FNAB for cytological analysis, which should decrease the incidence of the diagnosis of microcarcinomas (<1 cm).[3,108] Although there has been some controversy over the necessity and extent of surgery for microcarcinomas, new studies and treatment guidelines published over the past few years generally recommend surveillance or thyroid lobectomy for low-risk microcarcinomas rather than total thyroidectomy.[3,108-113] However, for low-risk, small (1-4 cm) DTC, the appropriate extent of surgery, whether it be total thyroidectomy or unilateral lobectomy, has been a longstanding subject of debate among experts.

Those in favor of total or near-total thyroidectomy argue that it may improve survival, reduce recurrence rates, and enable postoperative RAI therapy, although the indications for RAI ablation are decreasing. Total thyroidectomy allows for detection and removal of synchronous malignancies in the contralateral lobe, which occurs not infrequently given the multifocal tendency of thyroid cancer. As the initial operation, total thyroidectomy also has the benefit of limiting patients to a single procedure, whereas patients who undergo lobectomy may later require completion thyroidectomy based on pathology and staging. It was previously argued that complete removal of all thyroid tissue with total thyroidectomy and subsequent RAI facilitates postoperative follow-up for detection of residual or recurrent disease with whole body scanning or serum thyroglobulin (Tg) measurements. However, the use of whole body scanning in postoperative surveillance has fallen out of favor in recent years with the rise of ultrasonography. Even though RAI ablation is no longer recommended for low-risk DTC, the 2015 ATA guidelines for low-risk DTC patients who have undergone thyroid lobectomy or total thyroidectomy without RAI ablation continue to recommend periodic serum Tg measurements for postoperative follow-up.[3] Serum Tg measurements in patients who have not undergone RAI therapy can vary widely based on the amount of residual thyroid tissue and degree of TSH suppression.[114] Thus, it should not be surprising that there is more evidence to support the value of serum Tg levels in postoperative surveillance after total thyroidectomy without RAI,[115,116] whereas its value after lobectomy has been challenged in the most recent and extensive study on the subject to

date that demonstrated Tg levels and the Tg/TSH ratio increased gradually after lobectomy in patients with and without recurrences and therefore periodic measurements of serum Tg levels had limited value in predicting recurrent PTC after lobectomy.[117]

On the other hand, proponents of unilateral lobectomy for small low-risk tumors cite the benefits of less aggressive treatment, such as decreased risk of surgical complications and need for lifelong postoperative hormone replacement, although some patients may still require some degree of exogenous hormone replacement to maintain TSH suppression. Using data from the Healthcare Cost and Utilization Project-Nationwide Inpatient Sample (HCUP-NIS) from 1999 to 2003, 1 study found significantly higher rates of hypocalcemia and vocal cord palsy after total thyroidectomy vs lobectomy for thyroid cancer.[118] Another study based on the same HCUP-NIS database showed that despite the lower likelihood of complications seen in patients operated on by high volume vs low volume surgeons, the overall postoperative complication rate for total thyroidectomy was significantly higher when compared to lobectomy (20.4% vs 10.8%, respectively, $P < 0.0001$) for all surgeons, regardless of experience level, with hypocalcemia being the most common complication after either procedure. For high volume surgeons, the odds ratio of postoperative complication after bilateral vs unilateral thyroidectomy after adjusting for confounding factors was 1.824 (confidence interval 1.458-2.281, $P < 0.0001$).[119] It is argued that these benefits of unilateral lobectomy occur in the setting of similar overall survival rates as with total thyroidectomy despite the potential need for salvage therapy due to increased rates of recurrence.

A satisfactory resolution to this debate on surgical approach has proven elusive in part due to the lack of prospective, randomized controlled trials addressing this issue. Unfortunately, such a study would be nearly impossible to carry out given the excellent rates of disease-specific survival in DTC, at well over 90%,[120] and low overall incidence of recurrence, which would require impractically large numbers of subjects and lengthy follow-up time periods to demonstrate statistically significant differences. Although there have been a number of large-scale retrospective studies, they offer conflicting results which are difficult to compare given multiple variations in study design such as types of DTC included, use of lymph node dissection, use of adjuvant therapies such as RAI, and, perhaps most importantly, methods for patient selection for operations.

Guidelines regarding surgical treatment of 1-4 cm DTC have evolved over time based on the limited data available. In the prior ATA 2009 guidelines, near-total or total thyroidectomy was strongly recommended for all DTC larger than 1 cm.[121] The guidelines cited a study published in 2007 by Bilimoria and colleagues that reviewed 52,173 patients in the National Cancer Database (NCDB) who underwent surgery for PTC during the years 1985 to 1998. The study demonstrated higher overall survival for total thyroidectomy vs lobectomy (98.4% vs 97.1%, respectively, $P < 0.05$) and lower recurrence rates (7.7% vs 9.8%, respectively, $P < 0.05$),[122] although it has been debated whether these differences were actually clinically significant. In particular, they also focused on tumors at least 1 cm in size and found that lobectomy was associated with a 15% higher risk of recurrence ($P = 0.04$) and 31% higher risk of death ($P = 0.04$) when compared to total thyroidectomy.

Common criticisms of the 2007 study include a lack of disclosure regarding patient selection factors for performance of lobectomy vs total thyroidectomy, such as patient comorbidities and the presence of high-risk features. Aside from tumor size, other important confounding variables were not considered in their analysis. Later studies designed to address these criticisms place these findings into question. Using more recent NCDB data from 1998 to 2006, Adam and colleagues found a similar overall survival after total thyroidectomy vs lobectomy for PTC measuring 1-4 cm with multivariable analysis accounting for demographic factors including age, race and gender, extrathyroidal extension, multifocality, presence of nodal or distant metastases, RAI treatment, as well as stratification by tumor size.[123] Multiple studies have also looked at patients in the Surveillance, Epidemiology, and End Results database. Altogether, they found no significant differences between lobectomy and total thyroidectomy patients in 10-year overall or disease-specific survival, despite the inclusion of some high-risk patients in the studies.[124-126]

Most recently, a systematic review of 13 studies from 1990 to 2018 concluded that lobectomy resulted in similar oncologic outcomes as total thyroidectomy for small, low-risk PTC.[127] Three

of 5 included studies showed a small, statistically significant improvement in disease-free survival after total thyroidectomy.[122,128,129] In addition to the study by Bilimoria and colleagues, one involving 1685 patients treated at a single center from 1940 to 1991 revealed 20-year local recurrence and nodal metastases rates of 14% and 19%, respectively, with lobectomy as compared to 2% and 6% with total thyroidectomy ($P = 0.0001$).[129] However, these observed differences were not considered clinically significant in the review. This interpretation is supported by the fact that the majority of recurrences after lobectomy are locoregional, easily detected on follow-up, and treated with re-excision without significant impact on overall survival.[130-133]

The variation in recurrence rates reported in lobectomy patients for database studies also likely reflects the heterogeneity of patient selection methods for lobectomy in those populations. In contrast, low rates of locoregional recurrence and need for completion thyroidectomy after lobectomies, as well as excellent survival outcomes reported at the institutional level, may reflect the result of careful patient selection. For instance, Nixon and colleagues reported on 889 patients with T1T2N0 DTC treated with total thyroidectomy or thyroid lobectomy showing no significant difference in local recurrence (0% for total thyroidectomy and lobectomy) or regional recurrence (0.8% for total thyroidectomy and 0% for lobectomy, $P = 0.96$) with median follow-up of 99 months.[130]

Changes in the revised ATA 2015 guidelines reflect the results of these later studies. The new guidelines recommend either total thyroidectomy or unilateral lobectomy as sufficient initial treatment for DTC between 1 and 4 cm in size without clinical evidence of extrathyroidal extension or lymph node metastases.[3] The guidelines also list potential factors that would favor total thyroidectomy such as age greater than 45 years, contralateral thyroid nodules, personal history of head and neck radiation exposure, and familial DTC, as well as patient preference. Similar to the ATA guidelines, the 2018 National Comprehensive Cancer Network guidelines also recommend either total thyroidectomy or lobectomy for PTC in patients with no prior radiation exposure, no distant metastases, no cervical lymph node metastases, no extrathyroidal extension, and tumor size no greater than 4 cm in diameter[108] (Table 7).

Our evolving understanding of thyroid cancer has also resulted in a relatively recent change in surgical approach regarding a former histopathologic subtype of DTC. The follicular variant of PTC was previously characterized as a malignant neoplasm with follicles rather than papillae despite having nuclear features characteristic of PTC. It was previously subdivided into infiltrative (IFVPTC) and encapsulated (EFVPTC) subtypes.

Over the past few decades, the follicular variant of PTC has nearly tripled in incidence such that it surpassed classical PTC as the most common histologic finding in PTC.[134] The encapsulated subtype accounted for approximately one-half to two-thirds of the follicular variant of PTC.[135] At the same time, new research has revealed the largely indolent nature of the encapsulated subtype of the follicular variant[3,136-139] with high survival rates and low to absent rates of recurrence. Other studies did demonstrate the rare presence of distant metastases upon diagnosis or follow-up of patients with the encapsulated subtype.[140]

In 2016, an international retrospective review of 109 patients with the encapsulated subtype that were treated with total thyroidectomy or unilateral lobectomy without RAI ablation demonstrated 100% survival and no recurrence at time of last follow-up, which ranged from 10 to 26 years.[3] In order to discourage overly aggressive treatment of these indolent tumors, the study proposed that the encapsulated subtype be reclassified as noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP), a precancerous but nonmalignant entity separate from PTC.

These changes to distinguish NIFTP from its malignant counterparts were also in line with updated recommendations made previously by the 2015 ATA guidelines which suggested that EFVPTC tumors without known risk factors for malignancy such as thick capsule, tumor necrosis, or high mitotic activity can be adequately treated with lobectomy alone regardless of tumor size.[3] Of note, the guidelines emphasized the importance of careful pathologic evaluation to completely rule out the presence of invasive or infiltrative growth or the presence of areas of poorly differentiated carcinoma for the accurate diagnosis of NIFTP. Although the diagnosis of

Table 7
National guidelines for surgical approach to small (1-4 cm) low-risk differentiated thyroid cancer (DTC).

2019 ATA Guidelines	2015 ATA Guidelines	2018 NCCN Guidelines
Near-total or total thyroidectomy is recommended for thyroid cancer >1 cm, unless there are contraindications to this surgery.	Either bilateral procedure (near-total or total thyroidectomy) or a unilateral procedure (lobectomy) can be the initial treatment for patients with thyroid cancer >1 cm and <4 cm who meet the following criteria: • No extrathyroidal extension • No clinical evidence of any lymph node metastases (cN0) Additional criteria to consider for selecting a bilateral procedure over a unilateral one: • Older age (>45 years) • Presence of contralateral thyroid nodules or to address suspicions of bilateral disease • Personal history of radiation therapy to the head and neck • Familial DTC • Plans for RAI therapy or to facilitate follow-up strategies • Patient preference	Total thyroidectomy is recommended if any of the following criteria are present: • Tumor >4 cm in diameter • Known distant metastases • Extrathyroidal extension • Cervical lymph node metastases • Poorly differentiated • Consider for prior radiation exposure • Consider for bilateral nodularity If none of the first 5 of the above criteria are present, may consider either lobectomy or total thyroidectomy. The guidelines provide various evidence in support of each surgical approach without clearly advocating for one over the other, citing instead the importance of individualized consultation with each patient.

ATA, American Thyroid Association
NCCN, National Comprehensive Cancer Network
RAI, radioactive iodine.

NIFTP is a histologic one that requires lobectomy, subsequent completion thyroid lobectomy and RAI is not indicated once the diagnosis is made.

With the new recommendations supporting thyroid lobectomy for the treatment of NIFTP of all sizes, the ability to identify NIFTP preoperatively is increasingly important to avoid overtreatment of NIFTP with initial total thyroidectomy. In addition to ultrasound findings that indicate noninvasive tumor characteristics, both cytopathology and molecular profiling can be employed towards this goal. As discussed previously, the 2017 Bethesda system for thyroid cytopathology made various modifications to update the malignancy risk estimates for each diagnostic category where NIFTP is considered nonmalignant, which is especially useful in Bethesda III-V lesions which contain the largest proportion of cases of NIFTP.[44,141,142] Last, the new Bethesda system suggests including a note in the cytopathology report if there is any suspicion for NIFTP. Multiple cytomorphologic features have been shown to have statistically significant associations with NIFTP vs PTC.[142] The presence of these cytomorphologic features are not completely predictive of diagnosis of NIFTP on histopathology, but they still can play a role with other clinical findings to help guide surgical approach.

Aside from cytopathology, molecular profiling may also be used to help identify potential NIFTP tumors. In comparison to classical PTC, where *BRAF* mutations and *RET/PTC* rearrangements are the most commonly seen,[143] NIFTP tumors are more frequently characterized by *RAS* mutations and *PAX8/PPARG* rearrangements and rarely exhibit *BRAF* mutations.[144,145] Furthermore, a recent study found that 59% of surgically resected thyroid carcinomas with RAS mutations discovered on molecular profiling were found to be NIFTP in surgical pathology.[87] Given these findings, the reclassification of NIFTP as nonmalignant would likely alter performance measures from prior validation studies of molecular profiling where EFVPTC tumors were classified as malignant.[62,74,146-148] Moreover, the presence of RAS mutations should trigger a high suspicion for NIFTP which, interpreted in conjunction with other clinical findings, should impact

treatment selection. Ideally, the additional ability to distinguish NIFTP tumors from IFVPTC tumors would be useful in further stratification of surgical approach. Although *RAS* mutations are also commonly found in IFVPTC tumors, a portion of IFVPTC tumors have been shown to contain *BRAF* mutations instead.[144,145] However, this distinction is insufficient to accurately differentiate IFVPTC from NIFTP tumors in all cases and further work is required to determine other distinguishing characteristics.[141,149]

With increased use of unilateral lobectomy in the treatment of small low-risk DTC and NIFTP as a result of the new ATA guidelines, additional data should be available over the coming years to shed further light on this ongoing debate regarding the benefits and limitations of lobectomy vs total thyroidectomy. Separation of NIFTP from DTC moving forward will also remove an additional confounding factor in comparing the 2 operative strategies. As methods to better prognosticate thyroid cancer outcomes for individual tumors improve, we will likely see wider acceptance of unilateral lobectomy as an initial surgical approach in carefully selected patients with small, low-risk DTC.

Conclusion

Thyroid nodules are common and may be detected in up to 68% of the general population. Most thyroid nodules are benign, clinically insignificant, and are safely managed with a surveillance program. The main goal of initial and long-term follow-up is identification of the small subgroup of nodules that harbor a clinically significant cancer, cause compressive symptoms, are enlarging significantly, and/or progress to functional disease. A diagnostic algorithm that combines ultrasonography, FNAB, and molecular testing enables a personalized and safe approach to the management of thyroid nodules.

References

1. Force USPST, Bibbins-Domingo K, Grossman DC, et al. Screening for thyroid cancer: US Preventive Services Task Force Recommendation Statement. *JAMA*. 2017;317:1882–1887.
2. Grant EG, Tessler FN, Hoang JK, et al. Thyroid ultrasound reporting lexicon: white paper of the ACR Thyroid Imaging, Reporting and Data System (TIRADS) Committee. *J Am Coll Radiol*. 2015;12(12 Pt A):1272–1279.
3. Haugen BR, Alexander EK, Bible KC, 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;26:1–133.
4. Papini E, Guglielmi R, Bianchini A, et al. Risk of malignancy in nonpalpable thyroid nodules: predictive value of ultrasound and color-Doppler features. *J Clin Endocrinol Metab*. 2002;87:1941–1946.
5. Smith-Bindman R, Lebda P, Feldstein VA, et al. Risk of thyroid cancer based on thyroid ultrasound imaging characteristics: results of a population-based study. *JAMA Intern Med*. 2013;173:1788–1796.
6. Brito JP, Gionfriddo MR, Al Nofal A, et al. The accuracy of thyroid nodule ultrasound to predict thyroid cancer: systematic review and meta-analysis. *J Clin Endocrinol Metab*. 2014;99:1253–1263.
7. Kwak JY, Han KH, Yoon JH, et al. Thyroid imaging reporting and data system for US features of nodules: a step in establishing better stratification of cancer risk. *Radiology*. 2011;260:892–899.
8. Kim DS, Kim JH, Na DG, et al. Sonographic features of follicular variant papillary thyroid carcinomas in comparison with conventional papillary thyroid carcinomas. *J Ultrasound Med*. 2009;28:1685–1692.
9. Park YJ, Kim JA, Son EJ, et al. Thyroid nodules with macrocalcification: sonographic findings predictive of malignancy. *Yonsei Med J*. 2014;55:339–344.
10. Moon WJ, Jung SL, Lee JH, et al. Benign and malignant thyroid nodules: US differentiation–multicenter retrospective study. *Radiology*. 2008;247:762–770.
11. Machens A, Holzhausen HJ, Dralle H. The prognostic value of primary tumor size in papillary and follicular thyroid carcinoma. *Cancer*. 2005;103:2269–2273.
12. Cappelli C, Castellano M, Pirola I, et al. The predictive value of ultrasound findings in the management of thyroid nodules. *QJM*. 2007;100:29–35.
13. Moon HJ, Kwak JY, Kim MJ, Son EJ, Kim EK. Can vascularity at power Doppler US help predict thyroid malignancy? *Radiology*. 2010;255:260–269.
14. Horvath E, Majlis S, Rossi R, et al. An ultrasonogram reporting system for thyroid nodules stratifying cancer risk for clinical management. *J Clin Endocrinol Metab*. 2009;94:1748–1751.
15. Tae HJ, Lim DJ, Baek KH, et al. Diagnostic value of ultrasonography to distinguish between benign and malignant lesions in the management of thyroid nodules. *Thyroid*. 2007;17:461–466.
16. Shimura HHK, Hiejima Y, et al. Distinct diagnostic criteria for ultrasono- graphic examination of papillary thyroid carcinoma: a multicenter study. *Thyroid*. 2005;15:251–258.

17. Ito Y, Amino N, Yokozawa T, et al. Ultrasonographic evaluation of thyroid nodules in 900 patients: comparison among ultrasonographic, cytological, and histological findings. *Thyroid*. 2007;17:1269–1276.
18. 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;24:27–34.
19. Record Owner N.L.M. The value of fine-needle aspiration biopsy in patients with nodular thyroid disease divided into groups of suspicion of malignant neoplasms on clinical grounds.
20. Tessler FN, Middleton WD, Grant EG, et al. ACR Thyroid Imaging, Reporting and Data System (TI-RADS): white paper of the ACR TI-RADS committee. *J Am Coll Radiol*. 2017;14:587–595.
21. Middleton WD, Teefey SA, Reading CC, et al. Multiinstitutional analysis of thyroid nodule risk stratification using the American College of Radiology Thyroid Imaging Reporting and Data System. *AJR Am J Roentgenol*. 2017;208:1331–1341.
22. Tang AL, Falciglia M, Yang H, Mark JR, Steward DL. Validation of American Thyroid Association Ultrasound Risk Assessment of Thyroid Nodules Selected for Ultrasound Fine-Needle Aspiration. *Thyroid*. 2017;27:1077–1082.
23. Zheng Y, Xu S, Kang H, Zhan W. A single-center retrospective validation study of the American College of Radiology Thyroid Imaging Reporting and Data System. *Ultrasound Q*. 2018;34:77–83.
24. Maino F, Forleo R, Martinelli M, et al. Prospective validation of ATA and ETA sonographic pattern risk of thyroid nodules selected for FNAC. *J Clin Endocrinol Metab*. 2018;103:2362–2368.
25. Chng CL, Tan HC, Too CW, et al. Diagnostic performance of ATA, BTA and TIRADS sonographic patterns in the predication of malignancy in histologically proven thyroid nodules. *Singapore Med J*. 2018;59:578–583.
26. Yoon JH, Lee HS, Kim EK, Moon HJ, Kwak JY. Malignancy risk stratification of thyroid nodules: comparison between the Thyroid Imaging Reporting and Data System and the 2014 American Thyroid Association Management Guidelines. *Radiology*. 2016;278:917–924.
27. Nam-Goong IS, Kim HY, Gong G, et al. Ultrasonography-guided fine-needle aspiration of thyroid incidentaloma: correlation with pathological findings. *Clin Endocrinol*. 2004;60:21–28.
28. Chow SM, Law SC, Chan JK, Au SK, Yau S, Lau WH. Papillary microcarcinoma of the thyroid-prognostic significance of lymph node metastasis and multifocality. *Cancer*. 2003;98:31–40.
29. Grebe SK, Hay ID. Thyroid cancer nodal metastases: biologic significance and therapeutic considerations. *Surg Oncol Clin N Am*. 1996;5:43–63.
30. Scheumann GF, Gimm O, Wegener G, Hundeshagen H, Dralle H. Prognostic significance and surgical management of locoregional lymph node metastases in papillary thyroid cancer. *World J Surg*. 1994;18:559–567 discussion 567-558.
31. Ito Y, Uruno T, Nakano K, et al. An observation trial without surgical treatment in patients with papillary microcarcinoma of the thyroid. *Thyroid*. 2003;13:381–387.
32. Hay ID, Grant CS, van Heerden JA, Goellner JR, Ebersold JR, Bergstralh EJ. Papillary thyroid microcarcinoma: a study of 535 cases observed in a 50-year period. *Surgery*. 1992;112:1139–1146 discussion 1146-1137.
33. Qubain SW, Nakano S, Baba M, Takao S, Aikou T. Distribution of lymph node micrometastasis in pN0 well-differentiated thyroid carcinoma. *Surgery*. 2002;131:249–256.
34. Arturi F, Russo D, Giuffrida D, et al. Early diagnosis by genetic analysis of differentiated thyroid cancer metastases in small lymph nodes. *J Clin Endocrinol Metab*. 1997;82:1638–1641.
35. Solorzano CC, Carneiro DM, Ramirez M, Lee TM, Irvin 3rd GL. Surgeon-performed ultrasound in the management of thyroid malignancy. *Am Surg*. 2004;70:576–580 discussion 580-572.
36. Shimamoto K, Satake H, Sawaki A, Ishigaki T, Funahashi H, Imai T. Preoperative staging of thyroid papillary carcinoma with ultrasonography. *Eur J Radiol*. 1998;29:4–10.
37. Stulak JM, Grant CS, Farley DR, et al. Value of preoperative ultrasonography in the surgical management of initial and reoperative papillary thyroid cancer. *Arch Surg*. 2006;141:489–494 discussion 494-486.
38. Kouvaraki MA, Shapiro SE, Fornage BD, et al. Role of preoperative ultrasonography in the surgical management of patients with thyroid cancer. *Surgery*. 2003;134:946–954 discussion 954-945.
39. O'Connell K, Yen TW, Quiroz F, Evans DB, Wang TS. The utility of routine preoperative cervical ultrasonography in patients undergoing thyroidectomy for differentiated thyroid cancer. *Surgery*. 2013;154:697–701 discussion 701-693.
40. Leboulleux S, Girard E, Rose M, et al. Ultrasound criteria of malignancy for cervical lymph nodes in patients followed up for differentiated thyroid cancer. *J Clin Endocrinol Metab*. 2007;92:3590–3594.
41. Frasoldati A, Valcavi R. Challenges in neck ultrasonography: lymphadenopathy and parathyroid glands. *Endocr Pract*. 2004;10:261–268.
42. Kuna SK, Bracic I, Tesic V, Kuna K, Herceg GH, Dodig D. Ultrasonographic differentiation of benign from malignant neck lymphadenopathy in thyroid cancer. *J Ultrasound Med*. 2006;25:1531–1537 quiz 1538-1540.
43. Cibas ES, Ali SZ. The Bethesda system for reporting thyroid cytopathology. *Thyroid*. 2009;19:1159–1165.
44. Cibas ES, Ali SZ. The 2017 Bethesda system for reporting thyroid cytopathology. *Thyroid*. 2017;27:1341–1346.
45. Nikiforov YE, Seethala RR, Tallini G, et al. Nomenclature revision for encapsulated follicular variant of papillary thyroid carcinoma: a paradigm shift to reduce overtreatment of indolent tumors. *JAMA Oncol*. 2016;2:1023–1029.
46. Cesur M, Corapcioglu D, Bulut S, et al. Comparison of palpation-guided fine-needle aspiration biopsy to ultrasound-guided fine-needle aspiration biopsy in the evaluation of thyroid nodules. *Thyroid*. 2006;16:555–561.
47. Nou E, Kwong N, Alexander LK, Cibas ES, Marqusee E, Alexander EK. Determination of the optimal time interval for repeat evaluation after a benign thyroid nodule aspiration. *J Clin Endocrinol Metab*. 2014;99:510–516.
48. Medici M, Liu X, Kwong N, et al. Long- versus short-interval follow-up of cytologically benign thyroid nodules: a prospective cohort study. *BMC Med*. 2016;14:11.
49. Strickland KC, Howitt BE, Marqusee E, et al. The impact of noninvasive follicular variant of papillary thyroid carcinoma on rates of malignancy for fine-needle aspiration diagnostic categories. *Thyroid*. 2015;25:987–992.
50. Faquin WC, Wong LQ, Afrogheh AH, et al. Impact of reclassifying noninvasive follicular variant of papillary thyroid carcinoma on the risk of malignancy in the Bethesda system for reporting thyroid cytopathology. *Cancer Cytopathol*. 2016;124:181–187.

51. Cibas ES, Baloch ZW, Fellegara G, et al. A prospective assessment defining the limitations of thyroid nodule pathologic evaluation. *Ann Intern Med*. 2013;159:325–332.
52. Nayar R, Ivanovic M. The indeterminate thyroid fine-needle aspiration: experience from an academic center using terminology similar to that proposed in the 2007 National Cancer Institute Thyroid Fine Needle Aspiration State of the Science Conference. *Cancer*. 2009;117:195–202.
53. Ohori NP, Schoedel KE. Variability in the atypia of undetermined significance/follicular lesion of undetermined significance diagnosis in the Bethesda system for reporting thyroid cytopathology: sources and recommendations. *Acta Cytologica*. 2011;55:492–498.
54. Bongiovanni M, Spitale A, Faquin WC, Mazzucchelli L, Baloch ZW. The Bethesda system for reporting thyroid cytopathology: a meta-analysis. *Acta Cytologica*. 2012;56:333–339.
55. Cibas ES, Ali SZConference NCITFSotS. The Bethesda system for reporting thyroid cytopathology. *Am J Clin Pathol*. 2009;132:658–665.
56. Krauss EA, Mahon M, Fede JM, Zhang L. Application of the Bethesda classification for thyroid fine-needle aspiration: institutional experience and meta-analysis. *Arch Pathol Lab Med*. 2016;140:1121–1131.
57. Wang CC, Friedman L, Kennedy GC, et al. A large multicenter correlation study of thyroid nodule cytopathology and histopathology. *Thyroid*. 2011;21:243–251.
58. Eszlinger M, Lau L, Ghaznavi S, et al. Molecular profiling of thyroid nodule fine-needle aspiration cytology. *Nat Rev Endocrinol*. 2017;13:415–424.
59. Chudova D, Wilde JI, Wang ET, et al. Molecular classification of thyroid nodules using high-dimensionality genomic data. *J Clin Endocrinol Metab*. 2010;95:5296–5304.
60. Kloos RT. Molecular profiling of thyroid nodules: current role for the Afirma gene expression classifier on clinical decision making. *Mol Imaging Radionucl Ther*. 2017;26(Suppl 1):36–49.
61. Alexander EK, Kennedy GC, Baloch ZW, et al. Preoperative diagnosis of benign thyroid nodules with indeterminate cytology. *N Engl J Med*. 2012;367:705–715.
62. Harrell RM, Bimston DN. Surgical utility of Afirma: effects of high cancer prevalence and oncocytic cell types in patients with indeterminate thyroid cytology. *Endocr Pract*. 2014;20:364–369.
63. Marti JL, Avadhani V, Donatelli LA, et al. Wide inter-institutional variation in performance of a molecular classifier for indeterminate thyroid nodules. *Ann Surg Oncol*. 2015;22:3996–4001.
64. McIver B, Castro MR, Morris JC, et al. An independent study of a gene expression classifier (Afirma) in the evaluation of cytologically indeterminate thyroid nodules. *J Clin Endocrinol Metab*. 2014;99:4069–4077.
65. Alexander EK, Schorr M, Klopper J, et al. Multicenter clinical experience with the Afirma gene expression classifier. *J Clin Endocrinol Metab*. 2014;99:119–125.
66. McIver B. Evaluation of the thyroid nodule. *Oral Oncol*. 2013;49:645–653.
67. Duick DS, Klopper JP, Diggans JC, et al. The impact of benign gene expression classifier test results on the endocrinologist-patient decision to operate on patients with thyroid nodules with indeterminate fine-needle aspiration cytopathology. *Thyroid*. 2012;22:996–1001.
68. Sipos JA, Blevins TC, Shea HC, et al. Long-term nonoperative rate of thyroid nodules with benign results on the Afirma gene expression classifier. *Endocr Pract*. 2016;22:666–672.
69. Patel KN, Angell TE, Babiarz J, et al. Performance of a genomic sequencing classifier for the preoperative diagnosis of cytologically indeterminate thyroid nodules. *JAMA Surg*. 2018;153:817–824.
70. Ferraz C, Eszlinger M, Paschke R. Current state and future perspective of molecular diagnosis of fine-needle aspiration biopsy of thyroid nodules. *J Clin Endocrinol Metab*. 2011;96:2016–2026.
71. de Groot JW, Links TP, Plukker JT, Lips CJ, Hofstra RM. RET as a diagnostic and therapeutic target in sporadic and hereditary endocrine tumors. *Endocr Rev*. 2006;27:535–560.
72. Kondo T, Ezzat S, Asa SL. Pathogenetic mechanisms in thyroid follicular-cell neoplasia. *Nat Rev Cancer*. 2006;6:292–306.
73. Nikiforova MN, Lynch RA, Biddinger PW, et al. RAS point mutations and PAX8-PPAR gamma rearrangement in thyroid tumors: evidence for distinct molecular pathways in thyroid follicular carcinoma. *J Clin Endocrinol Metab*. 2003;88:2318–2326.
74. Nikiforov YE, Ohori NP, Hodak SP, 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;96:3390–3397.
75. Beaudenon-Huibregtse S, Alexander EK, Guttler RB, et al. Centralized molecular testing for oncogenic gene mutations complements the local cytopathologic diagnosis of thyroid nodules. *Thyroid*. 2014;24:1479–1487.
76. Eszlinger M, Bohme K, Ullmann M, et al. Evaluation of a two-year routine application of molecular testing of thyroid fine-needle aspirations using a seven-gene panel in a primary referral setting in Germany. *Thyroid*. 2017;27:402–411.
77. Zhang M, Lin O. Molecular testing of thyroid nodules: a review of current available tests for fine-needle aspiration specimens. *Arch Pathol Lab Med*. 2016;140:1338–1344.
78. Saji M, Ringel MD. The PI3K-Akt-mTOR pathway in initiation and progression of thyroid tumors. *Mol Cell Endocrinol*. 2010;321:20–28.
79. Cancer Genome Atlas Research Network. Integrated genomic characterization of papillary thyroid carcinoma. *Cell*. 2014;159:676–690.
80. Nikiforova MN, Wald AI, Roy S, Durso MB, Nikiforov YE. Targeted next-generation sequencing panel (ThyroSeq) for detection of mutations in thyroid cancer. *J Clin Endocrinol Metab*. 2013;98:E1852–E1860.
81. Nikiforov YE, Carty SE, Chiosea SI, 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;120:3627–3634.
82. Nikiforova MN, Mercurio S, Wald AI, et al. Analytical performance of the ThyroSeq v3 genomic classifier for cancer diagnosis in thyroid nodules. *Cancer*. 2018;124:1682–1690.

83. Kwak JY, Kim EK, Kim JK, et al. Dual priming oligonucleotide-based multiplex PCR analysis for detection of BRAFV600E mutation in FNAB samples of thyroid nodules in BRAFV600E mutation-prevalent area. *Head Neck*. 2010;32:490–498.
84. Lee SR, Jung CK, Kim TE, et al. Molecular genotyping of follicular variant of papillary thyroid carcinoma correlates with diagnostic category of fine-needle aspiration cytology: values of RAS mutation testing. *Thyroid*. 2013;23:1416–1422.
85. Gupta N, Dasyam AK, Carty SE, et al. RAS mutations in thyroid FNA specimens are highly predictive of predominantly low-risk follicular-pattern cancers. *J Clin Endocrinol Metab*. 2013;98:E914–E922.
86. Patel SG, Carty SE, McCoy KL, et al. Preoperative detection of RAS mutation may guide extent of thyroidectomy. *Surgery*. 2017;161:168–175.
87. Paulson VA, Shivdasani P, Angell TE, et al. Noninvasive follicular thyroid neoplasm with papillary-like nuclear features accounts for more than half of "carcinomas" harboring RAS mutations. *Thyroid*. 2017;27:506–511.
88. Stokowy T, Wojtas B, Jarzab B, et al. Two-miRNA classifiers differentiate mutation-negative follicular thyroid carcinomas and follicular thyroid adenomas in fine needle aspirations with high specificity. *Endocrine*. 2016;54:440–447.
89. Lodewijk L, Prins AM, Kist JW, et al. The value of miRNA in diagnosing thyroid cancer: a systematic review. *Cancer Biomark*. 2012;11:229–238.
90. Rossing M. Classification of follicular cell-derived thyroid cancer by global RNA profiling. *J Mol Endocrinol*. 2013;50:R39–R51.
91. Stokowy T, Wojtas B, Krajewska J, et al. A two miRNA classifier differentiates follicular thyroid carcinomas from follicular thyroid adenomas. *Mol Cell Endocrinol*. 2015;399:43–49.
92. Labourier E, Shifrin A, Busseniers AE, et al. Molecular testing for miRNA, mRNA, and DNA on fine-needle aspiration improves the preoperative diagnosis of thyroid nodules with indeterminate cytology. *J Clin Endocrinol Metab*. 2015;100:2743–2750.
93. Lithwick-Yanai G, Dromi N, Shtabsky A, et al. Multicentre validation of a microRNA-based assay for diagnosing indeterminate thyroid nodules utilising fine needle aspirate smears. *J Clin Pathol*. 2017;70:500–507.
94. Durante C, Costante G, Lucisano G, et al. The natural history of benign thyroid nodules. *JAMA*. 2015;313:926–935.
95. Kwak JY, Koo H, Youk JH, et al. Value of US correlation of a thyroid nodule with initially benign cytologic results. *Radiology*. 2010;254:292–300.
96. Rosario PW, Purisch S. Ultrasonographic characteristics as a criterion for repeat cytology in benign thyroid nodules. *Arq Bras Endocrinol Metabol*. 2010;54:52–55.
97. Chehade JM, Silverberg AB, Kim J, Case C, Mooradian AD. Role of repeated fine-needle aspiration of thyroid nodules with benign cytologic features. *Endocr Pract*. 2001;7:237–243.
98. Orlandi A, Puscar A, Capriata E, Fideleff H. Repeated fine-needle aspiration of the thyroid in benign nodular thyroid disease: critical evaluation of long-term follow-up. *Thyroid*. 2005;15:274–278.
99. Oertel YC, Miyahara-Felipe L, Mendoza MG, Yu K. Value of repeated fine needle aspirations of the thyroid: an analysis of over ten thousand FNAs. *Thyroid*. 2007;17:1061–1066.
100. Erdogan MF, Kamel N, Aras D, Akdogan A, Baskal N, Erdogan G. Value of re-aspirations in benign nodular thyroid disease. *Thyroid*. 1998;8:1087–1090.
101. Illouz F, Rodien P, Saint-Andre JP, et al. Usefulness of repeated fine-needle cytology in the follow-up of non-operated thyroid nodules. *Eur J Endocrinol*. 2007;156:303–308.
102. Jeong SH, Hong HS, Lee EH, Cha JG, Park JS, Kwak JJ. Outcome of thyroid nodules characterized as atypia of undetermined significance or follicular lesion of undetermined significance and correlation with Ultrasound features and BRAF(V600E) mutation analysis. *AJR Am J Roentgenol*. 2013;201:W854–W860.
103. Yoo WS, Choi HS, Cho SW, et al. The role of ultrasound findings in the management of thyroid nodules with atypia or follicular lesions of undetermined significance. *Clin Endocrinol*. 2014;80:735–742.
104. 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;20:3083–3088.
105. Kim DW, Lee EJ, Jung SJ, Ryu JH, Kim YM. Role of sonographic diagnosis in managing Bethesda class III nodules. *AJNR Am J Neuroradiol*. 2011;32:2136–2141.
106. Hay ID, Bergstralh EJ, Goellner JR, Ebersold JR, Grant CS. Predicting outcome in papillary thyroid carcinoma: development of a reliable prognostic scoring system in a cohort of 1779 patients surgically treated at one institution during 1940 through 1989. *Surgery*. 1993;114:1050–1057 discussion 1057-1058.
107. Brennan MD, Bergstralh EJ, van Heerden JA, McConahey WM. Follicular thyroid cancer treated at the Mayo Clinic, 1946 through 1970: initial manifestations, pathologic findings, therapy, and outcome. *Mayo Clin Proc*. 1991;66:11–22.
108. National Comprehensive Cancer Network. Thyroid Carcinoma (Version 1.2018). https://www.nccn.org/professionals/physician_gls/pdf/thyroid.pdf. Accessed August 28, 2018.
109. Lee J, Park JH, Lee CR, Chung WY, Park CS. Long-term outcomes of total thyroidectomy versus thyroid lobectomy for papillary thyroid microcarcinoma: comparative analysis after propensity score matching. *Thyroid*. 2013;23:1408–1415.
110. Kim SK, Park I, Woo JW, et al. Total thyroidectomy versus lobectomy in conventional papillary thyroid microcarcinoma: analysis of 8,676 patients at a single institution. *Surgery*. 2017;161:485–492.
111. Boucai L, Bernet V, Shaha A, Shindo ML, Stack BC, Tuttle RM. Surgical considerations for papillary thyroid microcarcinomas. *J Surg Oncol*. 2017;116:269–274.
112. Ito Y, Miyauchi A, Inoue H, et al. An observational trial for papillary thyroid microcarcinoma in Japanese patients. *World J Surg*. 2010;34:28–35.
113. Sugitani I, Toda K, Yamada K, Yamamoto N, Ikenaga M, Fujimoto Y. Three distinctly different kinds of papillary thyroid microcarcinoma should be recognized: our treatment strategies and outcomes. *World J Surg*. 2010;34:1222–1231.

114. Spencer CA, LoPresti JS, Fatemi S, Nicoloff JT. Detection of residual and recurrent differentiated thyroid carcinoma by serum thyroglobulin measurement. *Thyroid*. 1999;9:435–441.
115. Durante C, Montesano T, Attard M, et al. Long-term surveillance of papillary thyroid cancer patients who do not undergo postoperative radioiodine remnant ablation: is there a role for serum thyroglobulin measurement. *J Clin Endocrinol Metab*. 2012;97:2748–2753.
116. Nascimento C, Borget I, Troalen F, et al. Ultrasensitive serum thyroglobulin measurement is useful for the follow-up of patients treated with total thyroidectomy without radioactive iodine ablation. *Eur J Endocrinol*. 2013;169:689–693.
117. Park S, Jeon MJ, Oh HS, et al. Changes in serum thyroglobulin levels after lobectomy in patients with low-risk papillary thyroid cancer. *Thyroid*. 2018;28:997–1003.
118. Zerey M, Prabhu AS, Newcomb WL, Lincourt AE, Kercher KW, Heniford BT. Short-term outcomes after unilateral versus complete thyroidectomy for malignancy: a national perspective. *Am Surg*. 2009;75:20–24.
119. Hauch A, Al-Qurayshi Z, Randolph G, Kandil E. Total thyroidectomy is associated with increased risk of complications for low- and high-volume surgeons. *Ann Surg Oncol*. 2014;21:3844–3852.
120. Garas G, Jarral O, Tolley N, Palazzo F, Athanasiou T, Zacharakis E. Is there survival benefit from life-long follow-up after treatment for differentiated thyroid cancer? *Int J Surg*. 2013;11:116–121.
121. Cooper DS, Doherty GM, Haugen BR, et al. Revised American Thyroid Association management guidelines for patients with thyroid nodules and differentiated thyroid cancer. *Thyroid*. 2009;19:1167–1214.
122. Bilimoria KY, Bentrem DJ, Ko CY, et al. Extent of surgery affects survival for papillary thyroid cancer. *Ann Surg*. 2007;246:375–381 discussion 381-374.
123. Adam MA, Pura J, Gu L, et al. Extent of surgery for papillary thyroid cancer is not associated with survival: an analysis of 61,775 patients. *Ann Surg*. 2014;260:601–605 discussion 605-607.
124. Haigh PI, Urbach DR, Rotstein LE. Extent of thyroidectomy is not a major determinant of survival in low- or high-risk papillary thyroid cancer. *Ann Surg Oncol*. 2005;12:81–89.
125. Mendelsohn AH, Elashoff DA, Abemayor E, St John MA. Surgery for papillary thyroid carcinoma: is lobectomy enough. *Arch Otolaryngol Head Neck Surg*. 2010;136:1055–1061.
126. Barney BM, Hitchcock YJ, Sharma P, Shrieve DC, Tward JD. Overall and cause-specific survival for patients undergoing lobectomy, near-total, or total thyroidectomy for differentiated thyroid cancer. *Head Neck*. 2011;33:645–649.
127. Gartland RM, Lubitz CC. Impact of extent of surgery on tumor recurrence and survival for papillary thyroid cancer patients. *Ann Surg Oncol*. 2018;25:2520–2525.
128. Guo K, Wang Z. Risk factors influencing the recurrence of papillary thyroid carcinoma: a systematic review and meta-analysis. *Int J Clin Exp Pathol*. 2014;7:5393–5403.
129. Hay ID, Grant CS, Bergstralh EJ, Thompson GB, van Heerden JA, Goellner JR. Unilateral total lobectomy: is it sufficient surgical treatment for patients with AMES low-risk papillary thyroid carcinoma? *Surgery*. 1998;124:958–964 discussion 964-956.
130. Nixon IJ, Ganly I, Patel SG, et al. Thyroid lobectomy for treatment of well differentiated intrathyroid malignancy. *Surgery*. 2012;151:571–579.
131. Vaisman F, Shaha A, Fish S, Michael Tuttle R. 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;75:112–119.
132. Matsuzu K, Sugino K, Masudo K, et al. Thyroid lobectomy for papillary thyroid cancer: long-term follow-up study of 1,088 cases. *World J Surg*. 2014;38:68–79.
133. Kuba S, Yamanouchi K, Hayashida N, et al. Total thyroidectomy versus thyroid lobectomy for papillary thyroid cancer: comparative analysis after propensity score matching: a multicenter study. *Int J Surg*. 2017;38:143–148.
134. Jung CK, Little MP, Lubin JH, et al. The increase in thyroid cancer incidence during the last four decades is accompanied by a high frequency of BRAF mutations and a sharp increase in RAS mutations. *J Clin Endocrinol Metab*. 2014;99:E276–E285.
135. Proietti A, Giannini R, Ugolini C, et al. BRAF status of follicular variant of papillary thyroid carcinoma and its relationship to its clinical and cytological features. *Thyroid*. 2010;20:1263–1270.
136. Liu J, Singh B, Tallini G, et al. Follicular variant of papillary thyroid carcinoma: a clinicopathologic study of a problematic entity. *Cancer*. 2006;107:1255–1264.
137. Piana S, Frasoldati A, Di Felice E, Gardini G, Tallini G, Rosai J. Encapsulated well-differentiated follicular-patterned thyroid carcinomas do not play a significant role in the fatality rates from thyroid carcinoma. *Am J Surg Pathol*. 2010;34:868–872.
138. Chan J. Strict criteria should be applied in the diagnosis of encapsulated follicular variant of papillary thyroid carcinoma. *Am J Clin Pathol*. 2002;117:16–18.
139. Vivero M, Kraft S, Barletta JA. Risk stratification of follicular variant of papillary thyroid carcinoma. *Thyroid*. 2013;23:273–279.
140. Baloch ZW, LiVolsi VA. Encapsulated follicular variant of papillary thyroid carcinoma with bone metastases. *Mod Pathol*. 2000;13:861–865.
141. Zhao L, Dias-Santagata D, Sadow PM, Faquin WC. Cytological, molecular, and clinical features of noninvasive follicular thyroid neoplasm with papillary-like nuclear features versus invasive forms of follicular variant of papillary thyroid carcinoma. *Cancer Cytopathol*. 2017;125:323–331.
142. Brandler TC, Zhou F, Liu CZ, et al. Can noninvasive follicular thyroid neoplasm with papillary-like nuclear features be distinguished from classic papillary thyroid carcinoma and follicular adenomas by fine-needle aspiration. *Cancer Cytopathol*. 2017;125:378–388.
143. Cancer Genome Atlas Research Network. Integrated genomic characterization of papillary thyroid carcinoma. *Cell*. 2014;159:676–690.

144. Kim M, Jeon MJ, Oh HS, et al. BRAF and RAS mutational status in noninvasive follicular thyroid neoplasm with papillary-like nuclear features and invasive subtype of encapsulated follicular variant of papillary thyroid carcinoma in Korea. *Thyroid*. 2018;28:504–510.
145. Rivera M, Ricarte-Filho J, Knauf J, et al. Molecular genotyping of papillary thyroid carcinoma follicular variant according to its histological subtypes (encapsulated vs infiltrative) reveals distinct BRAF and RAS mutation patterns. *Mod Pathol*. 2010;23:1191–1200.
146. Nikiforov YE, Carty SE, Chiosea SI, 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;25:1217–1223.
147. Nikiforov YE. Role of molecular markers in thyroid nodule management: then and now. *Endocr Pract*. 2017;23:979–988.
148. Sahli ZT, Umbricht CB, Schneider EB, Zeiger MA. Thyroid nodule diagnostic markers in the face of the new NIFTP category: time for a reset. *Thyroid*. 2017;27:1393–1399.
149. Rosario PW. Ultrasonography and cytology as predictors of noninvasive follicular thyroid (NIFTP) neoplasm with papillary-like nuclear features: importance of the differential diagnosis with the invasive encapsulated follicular variant of papillary thyroid cancer. *Clin Endocrinol*. 2017;87:635–636.
150. Russ G, Bonnema SJ, Erdogan MF, Durante C, Ngu R, Leenhardt L. European Thyroid Association Guidelines for ultrasound malignancy risk stratification of thyroid nodules in adults: the EU-TIRADS. *Eur Thyroid J*. 2017;6:225–237.
151. Sohn YM, Kwak JY, Kim EK, Moon HJ, Kim SJ, Kim MJ. Diagnostic approach for evaluation of lymph node metastasis from thyroid cancer using ultrasound and fine-needle aspiration biopsy. *AJR Am J Roentgenol*. 2010;194:38–43.