

Evaluation and Management of Indeterminate Thyroid Nodules: The Revolution of Risk Stratification Beyond Cytological Diagnosis

Cancer Control
2017, Vol. 24(5) 1–14
© The Author(s) 2017
Reprints and permission:
sagepub.com/journalsPermissions.nav
DOI: 10.1177/1073274817729231
journals.sagepub.com/home/ccx



Pablo Valderrabano, MD, PhD¹ and Bryan McIver, MD, PhD¹

Abstract

In accordance with National Guidelines, we currently follow a linear approach to the diagnosis of thyroid nodules, with management decision based primarily on a cytological diagnosis following fine-needle aspiration biopsy. However, 25% of these biopsies render an indeterminate cytology, leaving uncertainty regarding appropriate management. Individualizing the risk of malignancy of these nodules could improve their management significantly. We summarize the current evidence on the relevance of clinical information, radiological features, cytological features, and molecular markers tests results and describe how these can be integrated to personalize the management of thyroid nodules with indeterminate cytology. Several factors can be used to stratify the risk of malignancy in thyroid nodules with indeterminate cytology. Male gender, large tumors (>4 cm), suspicious sonographic patterns, and the presence of nuclear atypia on the cytology are all associated with an increased cancer prevalence. The added value of current molecular markers in the risk stratification process needs further study because their performance seems compromised in some clinical settings and remains to be validated in others. Risk stratification is possible in thyroid nodules with indeterminate cytology using data that are often underused by current guidelines. Future guidelines should integrate these factors and personalize the recommended diagnostic and therapeutic approaches accordingly.

Keywords

thyroid nodule, diagnostic imaging, cytology, biomarkers, oncogenes, histology, differential diagnosis

Received December 22, 2016. Accepted for publication April 5, 2017.

Limitations and Opportunities of the Current Diagnostic Algorithm for the Evaluation of Thyroid Nodules

Most thyroid nodules are benign. However, thyroid cancer usually presents as a thyroid nodule. Establishing an adequate differential diagnosis is crucial to avoid unnecessary surgeries for asymptomatic benign nodules and delayed diagnosis and treatment for thyroid cancer. Current guidelines, including those from the American Thyroid Association (ATA), the American Association of Clinical Endocrinologists (AACE), American College of Endocrinology (ACE), and Associazione Medici Endocrinology (AME), the National Comprehensive Cancer Network (NCCN), and the British Thyroid Association (BTA) follow a linear approach to the diagnosis of thyroid nodules (Figure 1).^{1–4} After clinical and physical evaluation,

the sonographic appearance of the nodule is characterized to determine whether a biopsy is necessary or not and then rely almost exclusively on the cytological diagnosis to dictate management, supplemented increasingly by the results of one of several molecular marker tests. This general approach has been replicated consistently across professional association guidelines worldwide and has remained fundamentally unchanged

¹ Department of Head and Neck-Endocrine Oncology, H. Lee Moffitt Cancer Center & Research Institute, Tampa, FL, USA

Corresponding Author:

Pablo Valderrabano, Department of Head and Neck-Endocrine Oncology, H. Lee Moffitt Cancer Center & Research Institute, 12902 Magnolia Drive, FOB-2 H & N PROG, Tampa, FL 33612, USA.

Email: pablo.valderrabano@moffitt.org



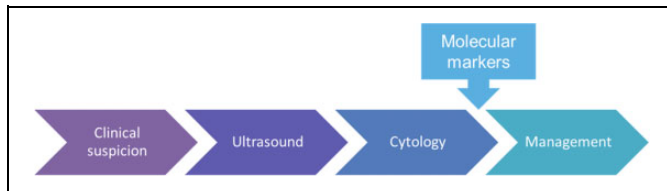


Figure 1. Current diagnostic approach for a newly diagnosed thyroid nodule.

for many years.¹⁻⁴ Nonetheless, it has a major drawback: approximately 25% of all thyroid biopsies do not render a definitive cytological diagnosis.⁵

We have known for many years, through population studies and autopsy series, that the prevalence of occult thyroid nodules and thyroid cancer is much higher than that which becomes clinically relevant.⁶⁻⁹ However, the rapid expansion of thyroid ultrasound use, both for diagnosis and for screening, has uncovered some of this reservoir of thyroid disease, contributing to a thyroid cancer “epidemic.”¹⁰ Indeed, thyroid cancer incidence is currently rising faster than any other cancer type; it is already the fifth most common cancer among women.¹¹ During 2016, approximately 64 300 new cases of thyroid cancer were diagnosed in the United States.¹² Despite these striking figures and the many challenges that this situation creates for any health-care system, thyroid cancer overdiagnosis likely represents the tip of an iceberg. Although the use of thyroid ultrasound and fine needle aspiration (FNA) biopsy continues to increase rapidly (5- and 7-fold increase in the last decade, respectively),¹³ the number of thyroid nodules with indeterminate cytology will follow those curves. In a recent meta-analysis, malignancies represented one-third of all resected nodules; half of all resected nodules had an indeterminate cytology; and two-thirds of them proved to be benign after a diagnostic surgery.⁵ Applying these figures to the number of thyroid cancers diagnosed (64 300) in 2016, we estimate that 192 900 biopsied nodules were resected in 2016 (64 300 cancers × 3); one-half of which (192 900/2 = 96 450) had indeterminate cytology and two-thirds of those ((96 450/3) × 2 = 64 300) ultimately proved to have benign histology. In summary, based on our current diagnostic approach, we removed approximately 64 300 thyroid cancers and approximately 64 300 benign thyroid nodules because of indeterminate cytology last year. This ongoing overtreatment exposes our patients to short- and long-term surgical complications, and many will face the need for life-long thyroid hormone replacement.¹⁴

This situation has underpinned the development of several molecular marker tests, in an attempt to refine the preoperative diagnosis to reduce the rate of diagnostic surgeries. These tests have been embraced with enthusiasm in parts of the United States and have already gained a prominent role in the recommended evaluation of thyroid nodules with indeterminate cytology in the 2015 ATA and 2015 NCCN guidelines.^{1,3} However, other professional association guidelines like those of AACE/ACE/AME and BTA are more cautious in

recommending the use of molecular markers for clinical use.^{2,4} This more conservative attitude is based on the lack of large prospective independent validation studies; the significant costs of molecular markers—presently most widely spread tests are >US\$5 000 per nodule—and their unknown long-term impact on health-care management and cost-effectiveness.

Nonetheless, molecular tests have made at least 1 valuable contribution: to make us aware of the need to individualize our assessment of a patient’s—and nodule’s—risk of malignancy, which underpins the interpretation of all subsequent tests.¹⁵ It is well recognized that the performance, and therefore the clinical utility, of molecular marker tests is highly dependent on the pretest risk of malignancy¹⁶; in this case, the prevalence of malignancy among thyroid nodules with indeterminate cytology, which varies widely among different institutions.¹⁷ However, analyzing the risk of malignancy of each indeterminate category in each institution is just the first necessary step toward the correct interpretation of these tests since many other factors impact on the individual pretest risk of malignancy of a given nodule.¹⁸ At the present time, most of these risk factors are used to alter the threshold for ultrasound evaluation and FNA biopsy but are largely ignored once cytology becomes available.¹⁻⁴ We review here how clinical, radiological, cytological, and molecular features impact on the risk of malignancy of thyroid nodules with indeterminate cytology; how can these features be integrated to optimize risk stratification.

Factors That Can Be Used for Risk Stratification of Indeterminate Thyroid Nodules

Clinical Characteristics

The evaluation of a patient with a known or suspected thyroid nodule begins with clinical history and physical evaluation.¹⁻⁴ Some risk factors, although infrequent, significantly raise the suspicion for malignancy and may push the clinician to recommend surgery, despite indeterminate cytology. Examples include the finding of cervical lymph node metastases; hard consistency on palpation, with fixation to adjacent structures; rapidly progressive and painful growth; rapid onset of compressive symptoms in the central neck, including dysphagia, dysphonia, or dyspnea; or the loss of recurrent laryngeal nerve function, suggesting locally invasive disease.¹⁹ Other risk factors modestly increase the risk of malignancy of thyroid nodules including: exposure to ionizing radiation, especially in childhood or adolescence; strong family history of first-degree relatives with thyroid cancer; male gender; solitary nodules; and nodule size >4 cm.²⁰ Several studies aimed to assess the impact of these factors on the risk of cancer of thyroid nodules with indeterminate cytology.

A recent meta-analysis of 19 studies, including 3494 patients with indeterminate thyroid nodules, showed that male gender and nodule size >4 cm were associated with an

increased risk of malignancy (odds ratio [OR]: 1.51 and 2.10, respectively).²¹ Nodule size was found to be an independent predictor of malignancy among mutation-negative nodules with atypia/follicular lesion of undetermined significance cytology in 1 study.²² In another study, the risk of cancer was found to be lowest for nodules 2.5 cm and increased 40% and 50% for each centimeter increase or decrease in size, respectively.²³ However, the impact of size on the risk of cancer of indeterminate thyroid nodules is still controversial due to conflicting data in other studies.²⁴ Family history of thyroid cancer and past history of radiation exposure seem not to significantly stratify the risk of malignancy of cytologically indeterminate thyroid nodules.^{23,25,26} The impact of single nodularity in risk stratification of indeterminate thyroid nodules is also unclear as it has been associated with increased, decreased, and no effect on the risk of malignancy.^{23,26-30}

Sonographic Features

Ultrasound plays a central role in the evaluation of thyroid nodules, identifying which nodules are worthy of biopsy. Some sonographic features have been consistently associated with an increased risk of malignancy including (from least to most specific): internal vascularity (OR ~ 3.5), solid composition (OR ~ 4.5), hypoechogenicity (OR ~ 5), irregular margins (OR approximately 6), microcalcifications (OR ~ 7), and shape taller than wide in the transverse view (OR ~ 10).^{20,31-33} Unfortunately, the heterogeneity in the published literature for the risk of malignancy associated with each feature is substantial; none of these sonographic features have sensitivity and specificity high enough to be clinically relevant in isolation.^{31,33} Furthermore, the features are subject to interpretation and influenced by external factors, such as imaging acquisition equipment, operator and settings, or screen resolution. As a result, the interobserver and intraobserver agreements for individual features are moderate (κ statistic of 0.4-0.6).³³⁻³⁵

Several classification systems have been developed to simplify the reporting of thyroid nodules and to guide the need for FNA biopsy. Each sonographic pattern is associated with an estimated risk of malignancy and their use seems to increase the interobserver agreement compared to individual sonographic features.^{36,37} Table 1 summarizes and compares the 2015 ATA sonographic patterns and those described in other classifications.^{1,2,4,38-44} Despite differences in number and nomenclature of sonographic patterns between classifications, all have demonstrated a significant gradation in the pretest risk of malignancy.^{1,2,4,38-44} More importantly, several studies, including ours, have demonstrated that these differences in the pretest risk of malignancy, do have a significant impact on the interpretation of the risk of malignancy of thyroid nodules with indeterminate cytology.⁴⁵⁻⁴⁹ Results are difficult to compare because the sonographic patterns, and the cytological diagnoses analyzed differ between studies, as does the underlying prevalence of malignancy, which ranges from 15% to 55%

(Table 2). However, cytologically indeterminate thyroid nodules with sonographic pattern equivalent to the ATA. “Very-low suspicion” had a prevalence of malignancy lower than other patterns in all studies, ranging from 4% to 22%; whereas those with sonographic pattern equivalent to the ATA “high suspicion” pattern had a prevalence of malignancy consistently higher than other patterns, ranging from 46% to 100%. Cytologically indeterminate thyroid nodules with sonographic patterns equivalent to the ATA “low suspicion” or “intermediate suspicion” had a prevalence of malignancy that ranged from 14% to 31% with overlapping results between these categories. Current guidelines recognize that the sonographic appearance should influence management to some extent. For example, a suspicious ultrasound in a nodule with benign cytology should trigger reevaluation and possible rebiopsy within a year; whereas nodules with benign appearance and benign cytology may not need any follow-up whatsoever.^{1,2,4} However, current guidelines do not yet recommend different management for cytologically indeterminate thyroid nodules with various sonographic patterns.¹⁻⁴ Based on recent data demonstrating the ability of sonographic patterns to stratify the risk of malignancy, we believe that these patterns should not only inform the selection of nodules for biopsy but also guide management after an indeterminate cytological diagnosis.

Additional Diagnostic Imaging Techniques

Thyroid nodules are one of the most frequent incidental findings reported on neck imaging studies that have been increasingly used in the last decades.^{50,51} Given that the prevalence of malignancy is not significantly different between palpable and nonpalpable nodules of the same size, many professional association guidelines recommend evaluating these incidental nodules with a dedicated thyroid ultrasound.^{1-3,52} Nonetheless, some guidelines, such as the BTA or the American College of Radiologists, are more restrictive in selecting incidental thyroid nodules detected during computed tomography or magnetic resonance imaging for full evaluation given the elevated prevalence of these findings.^{4,50} Even so, there is general agreement that incidental hypermetabolic thyroid nodules detected during ¹⁸F fluorodeoxyglucose positron emission tomography (PET) need further work-up with thyroid ultrasound and often biopsy as this finding is associated with an increased risk of cancer of around 35%.^{1-4,50,53} However, the impact of hypermetabolism on the interpretation of the risk of malignancy of thyroid cytology has been unclear. Our recent study on 436 biopsied thyroid nodules with PET scan and cytological evaluation demonstrated that the risk of malignancy increases with increasing maximum standardized uptake values (SUVmax) exceeding that of the general population (around 5%) at levels ≥ 2.5 .⁵⁴ This implies that nodules with SUVmax < 2.5 should probably receive the standard management, whereas higher SUVmax values have progressively increased suspicion for malignancy, which should arguably lower the size-threshold for biopsy.⁵⁴ The rate of aspirates diagnostic for malignancy

Table 1. 2015 American Thyroid Association Sonographic Patterns and Equivalence With Other Classifications.

Estimated PoM ¹	<1%	<3%	5%-10%	10%-20%	70%-90%
American Thyroid Association ^{1a}	Benign: Pure cyst	Very low suspicion: mixed spongiform	Low suspicion: solid + iso/hyperechoic	Intermediate suspicion: solid + hypoechoic	High suspicion: solid + hypoechoic + ≥1: - Microcalcifications - Irregular margins - Taller than wide - Disrupted rim calcification - ETE
K-TIRADS (Korean Society) ³⁸	2: Benign	2: Benign	3: Low suspicion	4: Intermediate suspicion	5: High suspicion
AACE/ACE/AME ^{2,a}	Low risk	Low risk	Intermediate risk	Intermediate risk	High risk
British Thyroid Association ^{4,a}	U2: Benign	U2: Benign	U2: Benign/ U3: Indeterminate/ Equivocal	U4: Suspicious	U4: Suspicious/ U5: Malignant
TIRADS (Russ) ³⁹	2: Benign	2: Benign	3: Very probably benign	4A: Mildly suspicious	Highly suspicious: 4B: 1-2 signs 5: 3 to 4 signs or LNM
TIRADS (Kwak) ⁴⁰	2: Benign	3: Probably benign	4A: Low suspicion for malignancy	4B: Intermediate suspicion for malignancy	4C: Moderate concern 5: Highly suggestive of malignancy
Park ⁴¹	TUS 1: Highly suggestive of benign	TUS 1: Highly suggestive of benign	TUS 2: Probably benign	TUS 3: Indeterminate	TUS 4: Probably malignant TUS 5: Highly suggestive of malignancy
TIRADS (Horvath) ⁴²	2: Benign findings	2: Benign findings	3 (if CLT): Probably benign 4A: Undetermined	3 (if CLT): Probably benign 4A: Undetermined	4B: Suspicious 5: Consistent with malignancy
Kuma Hospital ⁴³ Tae ⁴⁴	1: Benign Category 1: Benign	2: Benign Category 2: Benign	3: Borderline Category 2: Benign	3: Borderline Category 3: Malignant	4/5(if ETE): Malignant Category 3: Malignant

Abbreviations: AACE American Association of Clinical Endocrinologists; ACE, American College of Endocrinology; AME, Associazione Medici Endocrinology; CLT, chronic lymphocytic thyroiditis; ETE, extrathyroidal extension; LMN, lymph node metastasis; PoM, prevalence of malignancy; TIRADS, Thyroid Imaging Reporting and Data System.

^aClassifications without validation studies in which risk estimates were derived from previous classification systems.

Table 2. Risk Stratification of Indeterminate Thyroid Nodules According to Sonographic Pattern.

Publication	Kihara ⁴⁵		Jeong ⁴⁶		Russ ³⁹		Valderrabano ⁴⁷		Yoon ⁴⁸		Chng ⁴⁹	
Sonographic Classification	Kuma Hospital ⁴³		2011 Korean Society ¹¹⁵		TIRADS (Russ) ³⁹		ATA classification ¹		TIRADS (Kwak) ⁴⁰		TIRADS (Kwak) ⁴⁰	
Cytology group	Follicular tumors		B-III		B-III and IV		B-III and B-IV		B-III		B-IV	
	US Pattern (n)	PoM, % (n)	US Pattern, (n)	PoM, % (n)	US Pattern, (n)	PoM, % (n)	US Pattern, (n)	PoM, % (n)	US Pattern, (n)	PoM, % (n)	US Pattern (n)	PoM, % (n)
Low-risk patterns	1 (34)	9 (3)	Benign (0)	-	2 (0)	-	Very low (27)	4 (1)	3 (18)	22 (4)	3 (0)	-
Intermediate-risk patterns	2-3 (73)	19 (14)	Indeterminate (73)	25 (18)	3 (13)	15 (2)	Low (170)	25 (43)	4A (39)	31 (12)	4A (56)	14 (8)
High-risk patterns	4-5 (30)	53 (16)	Malignant (92)	79 (73)	4B (6)	33 (2)	Intermediate (36)	22 (8)	4B (41)	29 (12)	4B (78)	23 (18)
Overall ROM	24 (33/137)				5 (0)	-	High (134)	46 (61)	4C (79)	53 (42)	4C (8)	87 (7)
					15 (15/98)				5 (15)	80 (12)	5 (2)	100 (2)
									43 (82/192)		24 (35/144)	

Abbreviations: ATA, American Thyroid Association; Follicular tumors, equivalent to B-III and B-IV of the Bethesda system; B-III, Atypia/follicular lesion of undetermined significance (Bethesda category III); B-IV, Follicular/Hürthle cell neoplasm (Bethesda category IV); PoM, prevalence of malignancy; TIRADS: Thyroid Imaging Reporting and Data System, US pattern, sonographic pattern.

Table 3. Bethesda System for Reporting Thyroid Cytopathology and Equivalence With Other Classifications.

Bethesda System ⁵⁵	UK-Royal College of Pathologists ⁵⁶	Italian Consensus ⁵⁷	Japan Thyroid Association ⁵⁸
I-Nondiagnostic or unsatisfactory	Thy 1(c): nondiagnostic for cytological diagnosis (c: cystic lesion)	TIR 1(c): nondiagnostic (c: cystic)	1: Inadequate
II: Benign	Thy 2(c): Nonneoplastic (c: cystic lesion)	TIR 2: nonmalignant	2: Normal or benign
III: Atypia or follicular lesion of undetermined significance	Thy 3a: neoplasm possible-atypia/non-diagnostic	TIR3a: low-risk indeterminate lesion	3: Indeterminate A. Follicular neoplasms
IV: Follicular or Hürthle cell neoplasm	Thy 3f: neoplasm possible, suggesting follicular neoplasm	TIR3b: high-risk indeterminate lesion	A1. Favor benign A2. Borderline A3. Favor malignant B. Others (nonfollicular pattern lesions)
V: Suspicious for malignancy	Thy 4: suspicious for malignancy	TIR 4: suspicious for malignancy	4: Malignancy suspected
VI: Malignant	Thy 5: Malignant	TIR 5: Malignant	5: Malignancy

increased with increasing SUVmax values; but SUVmax values did not alter the risk of malignancy of thyroid cytopathology: all resected nodules with a benign cytology were benign; all but one with malignant or suspicious for malignancy cytology were malignant; and no discrimination threshold was clinically useful for nodules with indeterminate cytology.⁵⁴

Cytological Features

Cytological evaluation of a FNA biopsy specimen remains the most precise single test for the presurgical diagnosis of a thyroid nodule. Table 3 summarizes the equivalence of the categories of the Bethesda system for reporting thyroid cytopathology (Bethesda) and those in other classifications.⁵⁵⁻⁵⁸ A benign (B-II) or a malignant (B-VI) diagnosis carries a risk of malignancy of approximately <5% and >97%, respectively, making these categories very reliable.⁵⁵ Unfortunately, around 25% of FNA biopsies render an indeterminate cytological diagnosis.⁵ Indeterminate cytology is stratified into 3 categories in the Bethesda system: atypia or follicular lesion of undetermined significance (B-III), follicular or Hürthle cell neoplasm (B-IV), and suspicious for malignancy (B-V).⁵⁵ Each category was associated with an estimated risk of malignancy: 5% to 15%, 15% to 30%, and 60% to 75%, respectively.⁵⁵ These ranges in the risk of malignancy are used in current guidelines to recommend specific management for each category: repeat FNA in B-III, diagnostic lobectomy in B-IV, and lobectomy or total thyroidectomy in B-V.¹⁻⁴ However, the risk of malignancy of each category has much wider ranges in the published literature, ranging from 6% to 48% in B-III, 14% to 49% in B-IV, and 42% to 90% in B-V among different institutions.^{17,18} As a consequence, the risk of malignancy of these categories may overlap in some institutions, making it necessary to individualize management recommendations for each indeterminate category. For example, our recently published series from Moffitt Cancer Center (Tampa, Florida) demonstrated a risk of malignancy among resected nodules of 30% in B-III and 33% in B-IV.¹⁸

The variability in the risk of malignancy of indeterminate categories likely exists for several reasons,⁵⁹ although 3 of them are likely the most relevant:

- Differences in the application of diagnostic criteria for cytology among different observers and institutions. There is substantial overlap between cytological diagnostic categories.⁵⁹ This is particularly true for indeterminate categories where the interobserver agreement is much lower than for benign or malignant diagnoses.⁶⁰⁻⁶² The decision on whether to allocate a specific aspirate to one or the other category is subjective and dependent on the pathologist's training, experience, and local quality control. Second opinion or group consensus review has been shown to reduce the number of indeterminate aspirates and improve cytohistologic concordance, but inter-institutional agreement is likely to remain poor.⁶³⁻⁶⁵ Therefore, to optimize management recommendations, it is necessary to know the specific data for your institution/local pathologist.
- The heterogeneity of the specimens in the indeterminate categories. Indeterminate categories are very heterogeneous, particularly the B-III category. Therefore, it is likely that not all nodules within the same diagnostic category have the same risk of malignancy.^{59,66,67} For example, an aspirate with clotting artifact that creates tridimensional groups probably does not carry the same risk of malignancy as a nodule with mild or focal nuclear atypia suggestive of papillary thyroid carcinoma but insufficient to make a more definitive diagnosis, even though both scenarios are legitimately classified as B-III.⁵⁵ Several studies have attempted to refine the risk assessment by creating diagnostic subcategories.⁶⁶ In this regard, aspirates exhibiting mild/focal nuclear atypia have consistently exhibited a 2- to 3-fold higher risk of malignancy than other cytologically indeterminate thyroid nodules.⁶⁶ As a result, differences in the proportion of nodules with nuclear atypia within the indeterminate categories might explain, at least in

Table 4. Performance of Molecular Marker Tests as Reported in the Original Validation Studies.

Study Characteristics		n	PoM	Sn	Sp	PPV	NPV
Bethesda III (A/FLUS)							
Afirma ⁷⁶	Blinded, multicenter, prospective	129	24	90	53	38	95
miRInform ⁷⁷	Blinded, multicenter, prospective	22	50	36	82	67	56
miRInform +ThyraMIR ⁷⁸	Blinded, multicenter, prospective	58	NA	94	80	68	97
ThyroSeq v2 ⁸⁰	Not-blinded, single center, prospective	98	23	91	92	77	97
Bethesda IV (FN/HCN)							
Afirma ⁷⁶	Blinded, multicenter, prospective	81	25	90	49	37	94
miRInform ⁷⁷	Blinded, multicenter, prospective	19	32	67	92	80	86
miRInform +ThyraMIR ⁷⁸	Blinded, multicenter, prospective	51	NA	82	91	82	91
ThyroSeq v2 ⁷⁹	Not-blinded, single center, retrospective, and prospective	143	27	90	93	83	96

Abbreviations: A/FLUS, atypia follicular lesion of undetermined significance; FN/HCN, follicular neoplasm/Hurthle cell neoplasm; n, total number of nodules; NA, not applicable; NPV, negative predictive value; PoM, prevalence of malignancy; PPV, positive predictive value; Sn, sensitivity; Sp, specificity.

part, the interinstitutional differences observed for the prevalence of malignancy of these categories, particularly for B-III specimens.⁶⁶ Furthermore, cytological subcategories seem to be associated with distinct histological profiles.⁶⁷ Therefore, implementing standardized subcategories into the clinical practice should not only improve the cancer risk estimation but also the cytology–histology correlation, necessary to personalize management.

- Differences in the interpretation of borderline follicular lesions in histological specimens. The most frequent malignancy among thyroid nodules with indeterminate cytology is the follicular variant of papillary thyroid carcinoma (FVPTC).⁶⁸ The diagnosis of these tumors is often challenging and has low interobserver agreement, even among acknowledged experts. This is particularly true when the lesion is encapsulated, has no invasive features, and mild or focal areas of nuclear atypia.^{69,70} These lesions may be classified as either follicular adenomas with atypia—benign—or encapsulated noninvasive FVPTC—malignant—depending on the pathologist interpretation.⁷¹ Recently, a change in the nomenclature was proposed to recategorize well-defined noninvasive follicular pattern tumors with nuclear atypia as “noninvasive follicular thyroid neoplasm (NIFTP) with papillary-like nuclear features”.⁷² Recognizing the indolent behavior of these tumors, the new terminology eliminates the carcinoma label, but without truly defining them as benign, adding an additional layer of complexity to this challenging arena.⁷² At the same time, a nuclear-atypia score based on the qualitative assessment of 3 groups of nuclear features has been proposed to standardize the interpretation of nuclear atypia.⁷² However, the interpretation of these nuclear features is still subjective; significant differences between observers are expected.⁷² As a result of a stricter or less stringent threshold for considering the nuclear atypia “sufficient” for an NIFTP diagnosis, the estimated risk of malignancy within cytologically indeterminate thyroid nodules may be significantly impacted, if these lesions are considered malignant. In

contrast, if NIFTP are no longer considered malignant, the risk of malignancy of all indeterminate categories should decrease significantly^{73,74} and could reduce the variability in the risk of malignancy in cytology categories between institutions.

The interinstitutional variability in the risk of malignancy of indeterminate categories was of little relevance a few years ago because the expectation was that a diagnostic surgery would be performed in most of these nodules.⁷⁵ However, it has gained relevance in recent years because of its impact on the performance of molecular marker tests.¹⁶

Molecular Marker Tests

Several molecular marker tests have been commercialized in the United States in the last 5 years (Table 4).^{76–80} These can be classified according to their performance into 2 groups: Those able to achieve high positive predictive value (PPV), often referred to as “rule-in” tests for cancer; and those able to achieve high negative predictive value (NPV), often referred to as “rule-out” tests. The advantage of rule-in tests is to identify nodules that are most likely to be malignant, allowing an appropriate thyroid surgery to be planned from the outset, so reducing the need for a completion thyroidectomy.⁸¹ This advantage was more relevant when the treatment of choice for all thyroid cancers >1 cm was total thyroidectomy.⁷⁵ However, recent guidelines have moved to acknowledge that many intrathyroidal thyroid cancers <4 cm may be adequately treated with a lobectomy alone, which might change the perceived value of rule-in test.¹ In particular, lobectomy may be sufficient initial treatment for most FVPTCs and minimally invasive follicular thyroid carcinomas that represent a significant majority of the malignancies among indeterminate thyroid nodules.^{1,68}

Furthermore, currently available rule-in tests rely on the identification of somatic mutations known to drive cancer. Most of these mutations found in indeterminate cytology occur in the *RAS* gene.^{18,77,79–81} The prevalence of malignancy of *RAS*-mutant tumors has been usually quoted at

>80% in studies where histological interpretation was not blinded to molecular marker results, and the nuclear atypia interpretation was not standardized.^{82,83} However, most malignant *RAS*-mutant tumors are FVPTCs, particularly encapsulated and noninvasive (NIFTPs), that have very low malignant potential for which no further treatment is usually recommended after lobectomy limiting the clinical benefit of such finding preoperatively.^{18,72,82-84} Moreover, the cancer prevalence of *RAS*-mutant tumors in several other, more recent, studies has been lower, between 40% and 60% suggesting that it may have been previously overestimated.^{85,86} In our institution, *RAS*-mutations were associated with 53% (16/30 tumors) prevalence of cancer.^{18,87} However, the prevalence of invasive *RAS*-mutant cancers (20%, 6/30 tumors) was similar to that of other larger series (30%).⁸³ This finding suggests that differences in the classification of noninvasive neoplasms are responsible for the discrepancy in the risk of cancer of *RAS*-mutant tumors which significantly contributes to the overall PPV of oncogene panels that has been lower than previously reported.⁸⁷ Other more cancer-specific mutations such as *BRAF-V600E* are typically associated with full display of classical nuclear features and categorized as B-V or B-VI by cytopathologists but are infrequent among B-III or B-IV specimens.^{18,87-89}

The ATA recommends treating solitary, cytologically indeterminate, thyroid nodules with a lobectomy but suggests that total thyroidectomy might be more appropriate if a cancer-specific mutation is identified due to the higher prevalence of malignancy.¹ However, it has been recognized that mutations in *RAS*, the most frequent among nodules with indeterminate cytology, are usually associated with low-risk malignancies for which a lobectomy is often enough.⁹⁰ Therefore, current "rule-in" tests might have limited role in guiding the surgical extent of solitary indeterminate thyroid nodules.

The advantage of rule-out tests is to avoid surgery if an indeterminate thyroid nodule is classified by the test as benign with a false-negative rate approximately 5% or less (similar to that of a benign cytology).^{3,17} Despite promising initial results, the ability to rule out cancer with that level of confidence has not been adequately validated to date.⁷⁶ The resection rate of nodules that are molecularly "benign" has been disappointingly low in all of the independent clinical validation studies (generally <10% of benign calls and ≤5 nodules resected in most studies), which precludes the accurate calculation of NPV.⁹¹⁻⁹³

Moreover, it has been recently recognized by the ATA that the clinical utility of molecular marker tests (the NPV and PPV) is heavily influenced by the pretest risk of malignancy.¹⁶ Because clinical, sonographic, and cytological features influence the risk of malignancy of a given nodule beyond the cytological category, calculating the institutional prevalence of malignancy for each cytological category might be insufficient to adequately interpret molecular marker results.¹⁸ In general, molecular markers are considered of little benefit in cases with very high or very low risk of malignancy.¹⁶ For example, the risk of malignancy of indeterminate thyroid

nodules with high-suspicion sonographic pattern or nuclear atypia might be around 45% to 50%.^{47,66} Under these circumstances, none of the currently available molecular marker tests could, theoretically, achieve an NPV high enough to avoid surgery; whereas a positive result, despite increasing the risk of malignancy, is unlikely to change the clinical management given that a lobectomy is often sufficient in cytologically indeterminate thyroid nodules with a driver mutation (Figure 2).⁹⁰ Supporting this idea, a recent publication suggested that Afirma—a messenger RNA expression-based rule-out test—may not be useful in nodules with a repeated B-III cytology that are solid and hypoechoic on ultrasound scan because of the elevated pretest risk of malignancy in those nodules.⁹⁴ The performance of molecular marker tests (both rule-in and rule-out) in aspirates with oncocyctic cells seems to be particularly poor^{18,95-97}; whereas the performance in other subsets of indeterminate thyroid nodules is currently unknown. In our experience, oncogene panels performed worse than expected in B-III specimens perhaps due to differences in the cytological characteristics of specimens included in this category in ours and in previous studies.^{18,87}

The reclassification of NIFTPs as benign—nonmalignant—tumors is expected to decrease the prevalence of malignancy of the indeterminate cytology categories by 20% to 45%, particularly among specimens with mild or focal nuclear atypia or architectural atypia.^{67,73,74} This significant reduction in the pretest risk of malignancy is likely to increase the NPV and decrease the PPV of all molecular marker tests. However, the specific effect on these parameters will depend on the pathologist's NIFPT diagnostic threshold, the proportion of NIFTPs within the indeterminate categories, and the proportion of NIFTPs that are classified as "benign" or "suspicious" by each test, all of which are currently unknown.

Additional independent clinical validation studies are needed to assess the performance of all of the molecular marker tests, applied to specific subgroups of indeterminate thyroid nodules. Until those results are available, we must carefully select which test to apply to an individual nodule with indeterminate cytology, considering all other risk factors that might impact on the test performance.^{98,99} Indeterminate thyroid nodules that remain unresected on the basis of a rule-out test should be monitored carefully because the NPV of these tests has not been adequately validated. In that situation, the presence of suspicious clinical, sonographic, and/or cytological features, not just the nodule growth rate, should raise the concern about a false-negative result and lead to consideration of a repeat FNA biopsy.^{22,100}

Integration of Diagnostic Test Results

In our experience, the risk of malignancy of cytologically indeterminate thyroid nodules can be stratified using either sonographic patterns or cytological subcategories^{47,67} but is further refined when these variables are integrated (data not published, Figure 3). More importantly, the information provided by the sonographic features and cytological characteristics improve

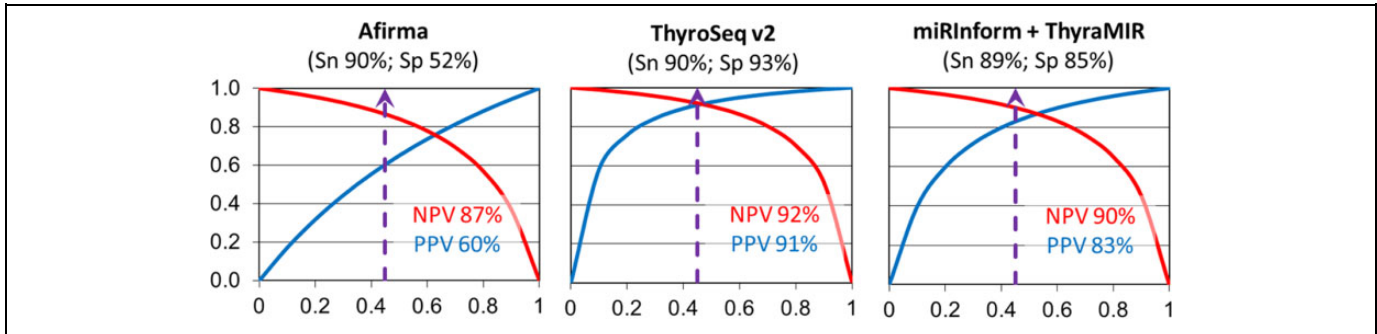


Figure 2. Theoretical performance of molecular marker tests for indeterminate thyroid nodules with either high-suspicion sonographic pattern or nuclear atypia. The sensitivity (Sn) and specificity (Sp) of the tests were calculated for cytologically indeterminate thyroid nodules (Bethesda III and IV) with the information provided in the original validation studies. The expected negative (solid red line) and positive (solid blue line) predictive values were calculated using a prevalence of malignancy of 45% (dashed purple line).^{77,79,80} NPV indicates negative predictive value; PPV, positive predictive value.

the prognostication of histological outcome.^{47,67} This information is necessary to optimize and to personalize management because it is likely to impact on the results of subsequent tests such as repeat biopsy or molecular marker tests.^{95,96,101,102} Our findings are supported by the results of several other studies.

Rosario stratified 150 B-III specimens using 2 risk factors: nuclear atypia and suspicious sonographic pattern.¹⁰² Nodules lacking both risk factors were associated with 4% prevalence of cancer, compared to 11% when only nuclear atypia was present, 47% when only suspicious ultrasound was present, and 87% when both factors were present.¹⁰² Rago et al created a score with clinical and sonographic features in which the weight of each feature was given based on its association with malignancy in a cohort of 505 indeterminate thyroid nodules.¹⁰³ The cancer risk in nodules with a score >7 was 41% compared to 16% in nodules with score ≤4. In both score groups, the cancer risk increased by approximately 20% when only nodules with nuclear atypia were analyzed (63% and 35%, respectively).¹⁰³ In a later publication from the same group on 1520 cytologically indeterminate thyroid nodules, they used a similar scoring system that integrated patient age, 3 sonographic features—hypoechoogenicity, irregular margins, and microcalcifications—and cytological category that stratified the risk of malignancy, from 17% in the lowest risk group to 64% in the highest risk group.⁶⁸ In addition, they found that the presence of more advanced or aggressive malignancies—which required more than surgery and ¹³¹I remnant ablation—was similarly stratified, with <1% of these malignancies within the lowest risk score group.⁶⁸

The McGill thyroid nodule score was developed by a single-center multidisciplinary team that included endocrinologists, otolaryngologists, surgeons, and pathologists.¹⁰⁴ A total of 22 variables including clinical, laboratory, radiological (ultrasound and PET), cytological, and molecular features were included in the score.¹⁰⁴ The relative weight of each variable was determined according to the estimated cancer risk of the variable and the supporting evidence in the literature, by consensus of the panel.¹⁰⁴ Varshney et al found that this score was lower for cytologically indeterminate

thyroid nodules with benign histology than that in nodules with malignant histology (7 and 9, respectively). The estimated cancer risk of those McGill scores were 32% and 63%, respectively ($P = .001$).¹⁰⁵

Others have created mathematical models with variables selected through multivariable logistic regression. The area under the receiver operating curve (AUC) is used to measure the discrimination ability of diagnostic models. An AUC of 1 indicates perfect discrimination, > 0.8 good discrimination, 0.6 to 0.8 moderate discrimination, and < 0.6 poor discrimination.¹⁰⁶ Banks et al developed a model in a retrospective cohort of 638 cytologically indeterminate thyroid nodules using 3 variables: patient age, nodule size, and cytological diagnosis that had an AUC of 0.74.²³ This model was validated in an independent cohort of 135 cytologically indeterminate thyroid nodules where it achieved an AUC of 0.85.²³ Patient age, nodule size, and cytological diagnosis were also used to develop a score that stratified the risk of malignancy. Scores <5 were associated with <25% cancer risk; scores 5 to 15 were associated with 25% to 75% cancer risk; and scores >15 were associated with >75% cancer risk.²³ Lubitz et al found that the best 3 variables to predict malignancy in a cohort of 144 follicular neoplasms were nodule size, and the presence of transgressing vessel or nuclear grooves on cytology. This model had, in their retrospective cohort, an AUC of 0.88.¹⁰⁷ Macias et al developed a model that integrated information on age, tobacco use, nodule size, presence of calcifications in ultrasound imaging, and nuclear atypia on cytology that had an AUC of 0.82 on 151 follicular neoplasms.²⁵ Lin et al developed a score system based on 3 variables: sonographic pattern, elastographic score, and cytological category that achieved an AUC of 0.87 on the 167 nodules of the study.²⁶

Artificial neural network analysis is a highly flexible non-linear regression model that uses machine learning algorithms inspired by the structural and functional aspects of neurons to integrate large sets of data and so generate a prediction of the probability of a specific event.¹⁰⁸ This approach has been used for different diagnostic and prognostic purposes in medicine. Ippolito et al used artificial neural network analysis to

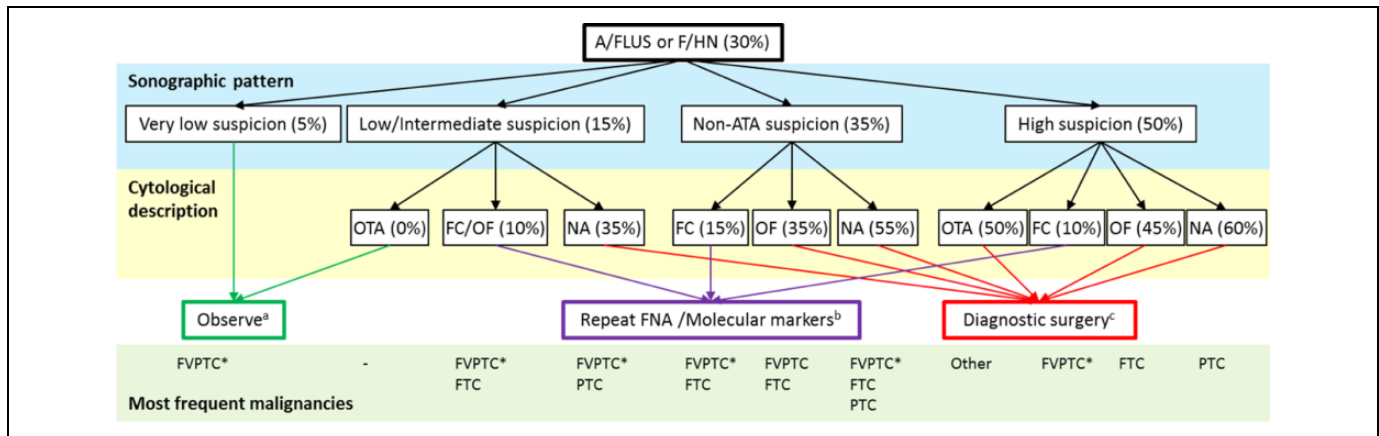


Figure 3. Proposed algorithm for evaluation and management of indeterminate thyroid nodules. Prevalence of malignancy in parenthesis and most frequent malignancies for each scenario derived from Moffitt retrospective data. Note that other institutions could have different findings. Non-ATA suspicion sonographic pattern includes heteroechoic nodules and iso or hyperechoic nodules with at least 1 suspicious sonographic feature. ^aConsider surgery if large (>4 cm), symptomatic or patient preference. Consider repeating FNA if cytological specimen was of limited quality (scant cellularity/ preparation artifact) in a solid nodule. ^bRepeat FNA is the preferred approach for A/FLUS unless management is already decided and unlikely to change with a different cytological diagnosis. Consider diagnostic surgery if large (>4 cm), symptomatic, patient preference, or if molecular markers are not available. Molecular markers could be helpful if surgery is not already indicated for other reasons, but their performance has not been validated in specific sonographic or cytologic scenarios, and negative results might need to be interpreted with caution. ^cIn the absence of other indications for total thyroidectomy, a lobectomy is usually appropriate for A/FLUS or F/HN even if mutations are identified with oncogene panels. Consider repeating biopsy before surgery in A/FLUS. A/FLUS indicates atypia/follicular lesion of undetermined significance, ATA, American Thyroid Association; FC, follicular cell predominance without nuclear atypia; FNA, fine needle aspiration; F/HN, follicular/Hürthle cell neoplasm; FTC, follicular thyroid carcinoma; FVPTC, follicular variant of papillary thyroid carcinoma, includes encapsulated noninvasive tumors (NIFTP, asterisk denotes when NIFTP are the most frequent tumors); NA, nuclear atypia; OF, oncocytic features; OTA, other types of atypia such as air drying or clotting artifacts, atypical lymphocytes, atypical cyst-lining cells, reactive changes. Other, nonfollicular cell-derived malignancies (in our series lymphoma); PTC, conventional papillary thyroid carcinoma.

develop a model in 371 cytologically indeterminate thyroid nodules that was validated in an independent set of 82 nodules.¹⁰⁹ They found that only certain cytological descriptors, but not clinical information, contributed to the model that performed better than standard cytological diagnosis alone, achieving an AUC of 0.88.¹⁰⁹ The work from Saylam et al suggests that models developed through artificial neural network analysis might be superior to multivariable logistic regression models.¹¹⁰ In their study on 116 cytological indeterminate thyroid nodules, the model developed through artificial neural network analysis achieved an AUC of 0.82 compared to 0.70 in that developed through multivariable logistic regression using the same variables.¹¹⁰

Interestingly, the AUC of commercialized molecular marker tests seems not to be superior to that of the models described above that use readily available information at no extra cost. In a recent publication describing our experience with ThyroSeq version 2, we found an AUC of 0.84 in the Bethesda IV category, where the performance was similar to the original validation study, whereas the AUC for Bethesda III specimens was significantly worse 0.57 ($P = 0.03$).⁸⁷ Unfortunately, none of the clinical risk assessment models have been subjected to independent validation studies that might support their generalization. Perhaps, this is due to the fact that each study has looked into different variables resulting in different algorithms. Most of them, however, incorporate some sonographic features—or patterns—and cytological features—often

presence of nuclear atypia—and frequently some other clinical or biochemical data.^{23,25,26,102,103,105,107} The impact of NIFTP reclassification on the performance of these models needs to be addressed.

Future Challenges and Perspectives

Noninvasive follicular thyroid neoplasms, are neither entirely benign, nor threatening malignancies, but rather tumors likely to be in a benign-to-malignant transformation.^{71,72,111,112} This concept, which applies to other thyroid neoplastic lesions also—like well-differentiated tumors of uncertain malignant potential, minimally invasive follicular thyroid carcinomas, or papillary microcarcinomas—renders the traditional dichotomous outcome of thyroid histology—“benign” or “malignant”—obsolete.¹¹³ As a consequence, NIFTP reclassification not only changes the nomenclature of some tumors but also constitutes acceptance of borderline/precursor lesions in the thyroid. In this context, B-III and B-IV are no longer indeterminate categories where we have benign or malignant tumors but rather categories that can accommodate these borderline/precursor follicular pattern lesions (Figure 4). The identification of more aggressive malignancies contaminating these categories seems to be appropriately performed through clinical risk assessment⁶⁸; but identifying borderline/precursor lesions contaminating higher risk cytological categories, particularly B-V, might be equally necessary to avoid

	Benign cytology	Indeterminate cytology	Malignant cytology
A.	Benign histology	Cancer	
B.	Benign histology	Borderline/Precursor lesions	Cancer

Figure 4. Thyroid cytology–histology correlation. (A) Traditional view of thyroid cytology–histology correlation. (B) Current view of thyroid cytology–histology correlation. Borderline/precursor lesions include neoplastic lesions without clear evidence of invasion or minimally invasive, with or without papillary-like nuclear features.

overdiagnosis and overtreatment.^{73,74,114} Therefore, we believe that it is time to incorporate clinical risk assessment tools/algorithms into the clinical practice to allow personalized management of cytologically indeterminate thyroid nodules. Molecular marker test results have also shown early promise in this regard. However, the use of both rule-in and rule-out tests should be applied, in our opinion, with caution because of the paucity of adequate independent clinical validation studies and the unknown impact on mid- and long-term clinical outcomes. Future professional guidelines need to face the challenge of changing the current linear diagnostic algorithm to one that integrates all relevant information before and after each diagnostic step. Standardizing reporting systems and the interpretation of sonographic and cytologic features will be key to generate generalizable models. Meanwhile, risk stratification of thyroid nodules with indeterminate cytology has proven feasible using clinical factors such as gender or nodule size; sonographic features, preferably grouped into sonographic patterns; and cytological features such as the presence/absence of nuclear atypia but needs to be tailored to the institutional outcomes.

Declaration of Conflicting Interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: No significant relationships exist between the authors and the companies/organizations whose products or services may be referenced in this article. Dr McIver receives grant/research support from GeneproDx. Dr Valderrabano has nothing to disclose.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

References

- 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):1-133.
- Gharib H, Papini E, Garber JR, et al. American Association of Clinical Endocrinologists, American College of Endocrinology, and Associazione Medici Endocrinologi Medical Guidelines for Clinical Practice for the Diagnosis and Management of Thyroid Nodules — 2016 Update. *Endocr Pract*. 2016;22(5):622-639.
- National Comprehensive Cancer Network. *NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines). Thyroid Carcinoma (version 2.2015)*. 2015. Accessed June 30, 2016.
- Perros P, Boelaert K, Colley S, et al. Guidelines for the management of thyroid cancer. *Clin Endocrinol (Oxf)*. 2014;81(suppl 1):1-122.
- Bongiovanni M, Spitale A, Faquin WC, Mazzucchelli L, Baloch ZW. The Bethesda system for reporting thyroid cytopathology: a meta-analysis. *Acta Cytol*. 2012;56(4):333-339.
- Mazzaferri EL. Management of a solitary thyroid nodule. *N Engl J Med*. 1993;328(8):553-559.
- Guth S, Theune U, Aberle J, Galach A, Bamberger CM. Very high prevalence of thyroid nodules detected by high frequency (13 MHz) ultrasound examination. *Eur J Clin Invest*. 2009;39(8):699-706.
- Mortensen JD, Woolner LB, Bennett WA. Gross and microscopic findings in clinically normal thyroid glands. *J Clin Endocrinol Metab*. 1955;15(10):1270-1280.
- Harach HR, Franssila KO, Wasenius VM. Occult papillary carcinoma of the thyroid. A “normal” finding in Finland. A systematic autopsy study. *Cancer*. 1985;56(3):531-538.
- Ahn HS, Kim HJ, Welch HG. Korea’s thyroid-cancer “epidemic”—screening and overdiagnosis. *N Engl J Med*. 2014;371(19):1765-1767.
- Siegel RL, Miller KD, Jemal A. Cancer statistics, 2016. *CA Cancer J Clin*. 2016;66(1):7-30.
- Howlander N, Noone AM, Krapcho M, et al. SEER Cancer Statistics Review, 1975-2013. National Cancer Institute. Bethesda, MD. http://seer.cancer.gov/csr/1975_2013/, based on November 2015 SEER data submission, posted to the SEER web site, April 2016. Accessed June 30, 2016.
- Zevallos JP, Hartman CM, Kramer JR, Sturgis EM, Chiao EY. Increased thyroid cancer incidence corresponds to increased use of thyroid ultrasound and fine-needle aspiration: a study of the veterans affairs health care system. *Cancer*. 2015;121(5):741-746.
- Bergenfels A, Jansson S, Kristofferson A, et al. Complications to thyroid surgery: results as reported in a database from a multicenter audit comprising 3,660 patients. *Langenbecks Arch Surg*. 2008;393(5):667-673.
- McIver B. Evaluation of the thyroid nodule. *Oral Oncol*. 2013;49(7):645-653.
- Ferris RL, Baloch Z, Bernet V, et al. American thyroid association statement on surgical application of molecular profiling for thyroid nodules: current impact on perioperative decision making. *Thyroid*. 2015;25(7):760-768.
- Wang CC, Friedman L, Kennedy GC, et al. A large multicenter correlation study of thyroid nodule cytopathology and histopathology. *Thyroid*. 2011;21(3):243-251.
- Valderrabano P, Leon ME, Centeno BA, et al. Institutional prevalence of malignancy of indeterminate thyroid cytology is

- necessary but insufficient to accurately interpret molecular marker tests. *Eur J Endocrinol.* 2016;174(5):621-629.
19. Hamming JF, Goslings BM, van Steenis GJ, van Ravenswaay Claasen H, Hermans J, van de Velde CJ. The value of fine-needle aspiration biopsy in patients with nodular thyroid disease divided into groups of suspicion of malignant neoplasms on clinical grounds. *Arch Intern Med.* 1990;150(1):113-116.
 20. Campanella P, Ianni F, Rota CA, Corsello SM, Pontecorvi A. Quantification of cancer risk of each clinical and ultrasonographic suspicious feature of thyroid nodules: a systematic review and meta-analysis. *Eur J Endocrinol.* 2014;170(5):R203-R211.
 21. Trimboli P, Treglia G, Guidobaldi L, et al. Clinical characteristics as predictors of malignancy in patients with indeterminate thyroid cytology: a meta-analysis. *Endocrine.* 2014;46(1):52-59.
 22. Mehta RS, Carty SE, Otori NP, et al. Nodule size is an independent predictor of malignancy in mutation-negative nodules with follicular lesion of undetermined significance cytology. *Surgery.* 2013;154(4):730-736; discussion 736-738.
 23. Banks ND, Kowalski J, Tsai HL, et al. A diagnostic predictor model for indeterminate or suspicious thyroid FNA samples. *Thyroid.* 2008;18(9):933-941.
 24. Varshney R, Forest VI, Zawawi F, et al. Ultrasound-guided fine-needle aspiration of thyroid nodules: does size matter? *Am J Otolaryngol.* 2014;35(3):373-376.
 25. Macias CA, Arumugam D, Arlow RL, et al. A risk model to determine surgical treatment in patients with thyroid nodules with indeterminate cytology. *Ann Surg Oncol.* 2015;22(5):1527-1532.
 26. Lin K, Xiang Y, Qiao L, Liu R, Dong S, Zhang X. A predictive model for selecting malignant thyroid nodules in patients with nondiagnostic or indeterminate fine-needle aspiration cytologic findings. *J Ultrasound Med.* 2015;34(7):1245-1251.
 27. Yoon JH, Lee HS, Kim EK, Moon HJ, Kwak JY. A nomogram for predicting malignancy in thyroid nodules diagnosed as atypia of undetermined significance/follicular lesions of undetermined significance on fine needle aspiration. *Surgery.* 2014;155(6):1006-1013.
 28. Raber W, Kaserer K, Niederle B, Vierhapper H. Risk factors for malignancy of thyroid nodules initially identified as follicular neoplasia by fine-needle aspiration: results of a prospective study of one hundred twenty patients. *Thyroid.* 2000;10(8):709-712.
 29. Tuttle RM, Lemar H, Burch HB. Clinical features associated with an increased risk of thyroid malignancy in patients with follicular neoplasia by fine-needle aspiration. *Thyroid.* 1998;8(5):377-383.
 30. Castro MR, Espiritu RP, Bahn RS, et al. Predictors of malignancy in patients with cytologically suspicious thyroid nodules. *Thyroid.* 2011;21(11):1191-1198.
 31. 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(4):1253-1263.
 32. Razavi SA, Hadduck TA, Sadigh G, Dwamena BA. Comparative effectiveness of elastographic and B-mode ultrasound criteria for diagnostic discrimination of thyroid nodules: a meta-analysis. *AJR Am J Roentgenol.* 2013;200(6):1317-1326.
 33. Remonti LR, Kramer CK, Leitao CB, Pinto LC, Gross JL. Thyroid ultrasound features and risk of carcinoma: a systematic review and meta-analysis of observational studies. *Thyroid.* 2015;25(5):538-550.
 34. Park CS, Kim SH, Jung SL, et al. Observer variability in the sonographic evaluation of thyroid nodules. *J Clin Ultrasound.* 2010;38(6):287-293.
 35. Moon WJ, Jung SL, Lee JH, et al. Benign and malignant thyroid nodules: US differentiation—multicenter retrospective study. *Radiology.* 2008;247(3):762-770.
 36. Valderrabano P, Klippenstein DL, Tourtelot JB, et al. New American Thyroid Association Sonographic Patterns for Thyroid Nodules Perform Well in Medullary Thyroid Carcinoma: Institutional Experience, Systematic Review, and Meta-Analysis. *Thyroid.* 2016;26(8):1093-1100.
 37. Cheng SP, Lee JJ, Lin JL, Chuang SM, Chien MN, Liu CL. Characterization of thyroid nodules using the proposed thyroid imaging reporting and data system (TI-RADS). *Head Neck.* 2013;35(4):541-547.
 38. Shin JH, Baek JH, Chung J, et al. Ultrasonography diagnosis and imaging-based management of thyroid nodules: Revised Korean Society of Thyroid Radiology Consensus Statement and Recommendations. *Korean J Radiol.* 2016;17(3):370-395.
 39. Russ G, Royer B, Bigorgne C, Rouxel A, Bienvenu-Perrard M, Leenhardt L. Prospective evaluation of thyroid imaging reporting and data system on 4550 nodules with and without elastography. *Eur J Endocrinol.* 2013;168(5):649-655.
 40. 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(3):892-899.
 41. Park JY, Lee HJ, Jang HW, et al. A proposal for a thyroid imaging reporting and data system for ultrasound features of thyroid carcinoma. *Thyroid.* 2009;19(11):1257-1264.
 42. 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(5):1748-1751.
 43. 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(12):1269-1276.
 44. 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(5):461-466.
 45. Kihara M, Ito Y, Hirokawa M, et al. Role of ultrasonography in patients with cytologically follicular thyroid tumor. *Auris Nasus Larynx.* 2011;38(4):508-511.
 46. 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(6):W854-W860.
 47. Valderrabano P, Klippenstein DL, Centeno BA, Leon ME, McIver B. Sonographic pattern stratifies the risk of malignancy of

- thyroid nodules with indeterminate cytology 2015 Abstracts. Abstract 1003. *Endocrine Pract.* 2015;21(suppl 2):1-257.
48. Yoon JH, Kwon HJ, Kim EK, Moon HJ, Kwak JY. Subcategorization of atypia of undetermined significance/follicular lesion of undetermined significance (AUS/FLUS): a study applying Thyroid Imaging Reporting and Data System (TIRADS). *Clin Endocrinol (Oxf)*. 2016;85(2):275-282.
 49. Chng CL, Kurzawinski TR, Beale T. Value of sonographic features in predicting malignancy in thyroid nodules diagnosed as follicular neoplasm on cytology. *Clin Endocrinol (Oxf)*. 2015; 83(5):711-716.
 50. Hoang JK, Langer JE, Middleton WD, et al. Managing incidental thyroid nodules detected on imaging: white paper of the ACR Incidental Thyroid Findings Committee. *J Am Coll Radiol*. 2015;12(2):143-150.
 51. Lang K, Huang H, Lee DW, Federico V, Menzin J. National trends in advanced outpatient diagnostic imaging utilization: an analysis of the medical expenditure panel survey, 2000-2009. *BMC Med Imaging*. 2013;13:40.
 52. Hagag P, Strauss S, Weiss M. Role of ultrasound-guided fine-needle aspiration biopsy in evaluation of nonpalpable thyroid nodules. *Thyroid*. 1998;8(11):989-995.
 53. Soelberg KK, Bonnema SJ, Brix TH, Hegedus L. Risk of malignancy in thyroid incidentalomas detected by 18F-fluorodeoxyglucose positron emission tomography: a systematic review. *Thyroid*. 2012;22(9):918-925.
 54. Valderrabano P, Montilla-Soler J, Mifsud M, et al. Hypermetabolism on (18)F-fluorodeoxyglucose positron emission tomography scan does not influence the interpretation of thyroid cytopathology, and nodules with a SUVmax <2.5 are not at increased risk for malignancy. *Thyroid*. 2016;26(9):1300-1307.
 55. Cibas ES, Ali SZ. The Bethesda system for reporting thyroid cytopathology. *Thyroid*. 2009;19(11):1159-1165.
 56. The Royal College of Pathologists. Guidance on the reporting of thyroid cytology specimens. 2016. <https://www.rcpath.org/resourceLibrary/g089-guidancereportingthyroidcytology-jan16.html>. Accessed July 15, 2016.
 57. Nardi F, Basolo F, Crescenzi A, et al. Italian consensus for the classification and reporting of thyroid cytology. *J Endocrinol Invest*. 2014;37(6):593-599.
 58. Kakudo K, Kameyama K, Miyauchi A, Nakamura H. Introducing the reporting system for thyroid fine-needle aspiration cytology according to the new guidelines of the Japan thyroid association. *Endocr J*. 2014;61(6):539-552.
 59. Otori 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 Cytol*. 2011;55(6):492-498.
 60. Cibas ES, Baloch ZW, Fellegara G, et al. A prospective assessment defining the limitations of thyroid nodule pathologic evaluation. *Ann Intern Med*. 2013;159(5):325-332.
 61. Olson MT, Boonyarunnate T, Aragon Han P, Umbricht CB, Ali SZ, Zeiger MA. A tertiary center's experience with second review of 3885 thyroid cytopathology specimens. *J Clin Endocrinol Metab*. 2013;98(4):1450-1457.
 62. Bajaj J, Morgenstern N, Sugrue C, Wasserman J, Wasserman P. Clinical impact of second opinion in thyroid fine needle aspiration cytology (FNAC): a study of 922 interinstitutional consultations. *Diagn Cytopathol*. 2012;40(5):422-429.
 63. Jing X, Knoepp SM, Roh MH, et al. Group consensus review minimizes the diagnosis of "follicular lesion of undetermined significance" and improves cytohistologic concordance. *Diagn Cytopathol*. 2012;40(12):1037-1042.
 64. Gerhard R, Boerner SL. The value of second opinion in thyroid cytology: a review. *Cancer Cytopathol*. 2014;122(8):611-619.
 65. Davidov T, Trooskin SZ, Shanker BA, et al. Routine second-opinion cytopathology review of thyroid fine needle aspiration biopsies reduces diagnostic thyroidectomy. *Surgery*. 2010; 148(6):1294-1299; discussion 1299-1301.
 66. Nishino M, Wang HH. Should the thyroid AUS/FLUS category be further stratified by malignancy risk? *Cancer Cytopathol*. 2014;122(7):481-483.
 67. Valderrabano P, Khazai L, Thompson ZJ, et al. Cancer risk stratification for indeterminate thyroid nodules: a cytological approach. *Thyroid*. 2017. doi: 10.1089/thy.2017.0221. [Epub ahead of print].
 68. Rago T, Scutari M, Latrofa F, et al. The large majority of 1520 patients with indeterminate thyroid nodule at cytology have a favorable outcome, and a clinical risk score has a high negative predictive value for a more cumbersome cancer disease. *J Clin Endocrinol Metab*. 2014;99(10):3700-3707.
 69. Lloyd RV, Erickson LA, Casey MB, et al. Observer variation in the diagnosis of follicular variant of papillary thyroid carcinoma. *Am J Surg Pathol*. 2004;28(10):1336-1340.
 70. Hirokawa M, Carney JA, Goellner JR, et al. Observer variation of encapsulated follicular lesions of the thyroid gland. *Am J Surg Pathol*. 2002;26(11):1508-1514.
 71. Kakudo K, Bai Y, Liu Z, Ozaki T. Encapsulated papillary thyroid carcinoma, follicular variant: a misnomer. *Pathol Int*. 2012;62(3): 155-160.
 72. 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(8):1023-1029.
 73. 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(3):181-187.
 74. 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(9):987-992.
 75. 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(11):1167-1214.
 76. Alexander EK, Kennedy GC, Baloch ZW, et al. Preoperative diagnosis of benign thyroid nodules with indeterminate cytology. *N Engl J Med*. 2012;367(8):705-715.
 77. 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(10):1479-1487.
78. 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(7):2743-2750.
 79. 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(23):3627-3634.
 80. 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(11):1217-1223.
 81. 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(11):3390-3397.
 82. 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(5):E914-E922.
 83. Radkay LA, Chiosea SI, Seethala RR, et al. Thyroid nodules with KRAS mutations are different from nodules with NRAS and HRAS mutations with regard to cytopathologic and histopathologic outcome characteristics. *Cancer Cytopathol*. 2014;122(12):873-882.
 84. Paulson VA, Shivdasani P, Angell TE, et al. Noninvasive follicular thyroid neoplasm with papillary-like nuclear features accounts for over half of "carcinomas" harboring RAS mutations. *Thyroid*. 2017;27(4):506-511.
 85. Eszlinger M, Piana S, Moll A, et al. Molecular testing of thyroid fine-needle aspirations improves presurgical diagnosis and supports the histologic identification of minimally invasive follicular thyroid carcinomas. *Thyroid*. 2015;25(4):401-409.
 86. Krane JF, Cibas ES, Alexander EK, Paschke R, Eszlinger M. Molecular analysis of residual ThinPrep material from thyroid FNAs increases diagnostic sensitivity. *Cancer Cytopathol*. 2015;123(6):356-361.
 87. Valderrabano P, Khazai L, Leon ME, et al. Evaluation of ThyroSeq v2 performance in thyroid nodules with indeterminate cytology. *Endocr Relat Cancer*. 2017;24(3):127-136.
 88. Kleiman DA, Sporn MJ, Beninato T, et al. Preoperative BRAF(V600E) mutation screening is unlikely to alter initial surgical treatment of patients with indeterminate thyroid nodules: a prospective case series of 960 patients. *Cancer*. 2013;119(8):1495-1502.
 89. Trimboli P, Treglia G, Condorelli E, et al. BRAF-mutated carcinomas among thyroid nodules with prior indeterminate FNA report: a systematic review and meta-analysis. *Clin Endocrinol (Oxf)*. 2016;84(3):315-320.
 90. Patel SG, Carty SE, McCoy KL, et al. Preoperative detection of RAS mutation may guide extent of thyroidectomy. *Surgery*. 2017;161(1):168-175.
 91. Singer J, Hanna JW, Visaria J, Gu T, McCoy M, Kloos RT. Impact of a gene expression classifier on the long-term management of patients with cytologically indeterminate thyroid nodules. *Curr Med Res Opin*. 2016;32(7):1225-1232.
 92. 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(6):666-672.
 93. Nishino M. Molecular cytopathology for thyroid nodules: a review of methodology and test performance. *Cancer Cytopathol*. 2016;124(1):14-27.
 94. Villabona CV, Mohan V, Arce KM, et al. Utility of ultrasound vs. Gene expression classifier in thyroid nodules with atypia of undetermined significance. *Endocr Pract*. 2016;22(10):1199-1203.
 95. Harrell RM, Bimston DN. Surgical utility of afirma: effects of high cancer prevalence and oncocyctic cell types in patients with indeterminate thyroid cytology. *Endocr Pract*. 2014;20(4):364-369.
 96. Brauner E, Holmes BJ, Krane JF, et al. Performance of the afirma gene expression classifier in Hurthle cell thyroid nodules differs from other indeterminate thyroid nodules. *Thyroid*. 2015;25(7):789-796.
 97. 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(11):E1852-E1860.
 98. Noureldine SI, Olson MT, Agrawal N, Prescott JD, Zeiger MA, Tufano RP. Effect of gene expression classifier molecular testing on the surgical decision-making process for patients with thyroid nodules. *JAMA Otolaryngol Head Neck Surg*. 2015;141(12):1082-1088.
 99. Sacks WL, Bose S, Zumsteg ZS, et al. Impact of afirma gene expression classifier on cytopathology diagnosis and rate of thyroidectomy. *Cancer*. 2016;124(10):722-728.
 100. Nakamura H, Hirokawa M, Ota H, Kihara M, Miya A, Miyauchi A. Is an increase in thyroid nodule volume a risk factor for malignancy? *Thyroid*. 2015;25(7):804-811.
 101. Hyeon J, Ahn S, Shin JH, Oh YL. The prediction of malignant risk in the category "atypia of undetermined significance/follicular lesion of undetermined significance" of the Bethesda System for Reporting Thyroid Cytopathology using subcategorization and BRAF mutation results. *Cancer Cytopathol*. 2014;122(5):368-376.
 102. Rosario PW. Thyroid nodules with atypia or follicular lesions of undetermined significance (Bethesda Category III): importance of ultrasonography and cytological subcategory. *Thyroid*. 2014;24(7):1115-1120.
 103. Rago T, Di Coscio G, Basolo F, et al. Combined clinical, thyroid ultrasound and cytological features help to predict thyroid malignancy in follicular and Hupsilonrthle cell thyroid lesions: results from a series of 505 consecutive patients. *Clin Endocrinol (Oxf)*. 2007;66(1):13-20.
 104. Sands NB, Karls S, Amir A, et al. McGill Thyroid Nodule Score (MTNS): "rating the risk," a novel predictive scheme for cancer risk determination. *J Otolaryngol Head Neck Surg*. 2011;40(suppl 1):S1-S13.
 105. Varshney R, Forest VI, Mascarella MA, et al. The McGill thyroid nodule score—does it help with indeterminate thyroid nodules? *J Otolaryngol Head Neck Surg*. 2015;44:2.

106. Hanley JA, McNeil BJ. The meaning and use of the area under a receiver operating characteristic (ROC) curve. *Radiology*. 1982;143(1):29-36.
107. Lubitz CC, Faquin WC, Yang J, et al. Clinical and cytological features predictive of malignancy in thyroid follicular neoplasms. *Thyroid*. 2010;20(1):25-31.
108. Dybowski R, Gant V. Artificial neural networks in pathology and medical laboratories. *Lancet*. 1995;346(8984):1203-1207.
109. Ippolito AM, De Laurentiis M, La Rosa GL, et al. Neural network analysis for evaluating cancer risk in thyroid nodules with an indeterminate diagnosis at aspiration cytology: identification of a low-risk subgroup. *Thyroid*. 2004;14(12):1065-1071.
110. Saylam B, Keskek M, Ocak S, Akten AO, Tez M. Artificial neural network analysis for evaluating cancer risk in multinodular goiter. *J Res Med Sci*. 2013;18(7):554-557.
111. 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(6):868-872.
112. Ganly I, Wang L, Tuttle RM, et al. Invasion rather than nuclear features correlates with outcome in encapsulated follicular tumors: further evidence for the reclassification of the encapsulated papillary thyroid carcinoma follicular variant. *Hum Pathol*. 2015;46(5):657-664.
113. Kakudo K, Bai Y, Liu Z, Li Y, Ito Y, Ozaki T. Classification of thyroid follicular cell tumors: with special reference to borderline lesions. *Endocr J*. 2012;59(1):1-12.
114. Maletta F, Massa F, Torregrossa L, et al. Cytological features of "noninvasive follicular thyroid neoplasm with papillary-like nuclear features" and their correlation with tumor histology. *Hum Pathol*. 2016;54:134-142.
115. Moon WJ. Imaging diagnosis. In: Thyroid Study Group of Head and Neck Society of Korean Radiology, ed. *Thyroid Imaging, Diagnosis and Intervention*. 1st ed. Seoul, Korea: Ilchokak; 2008:150-183.