Thyroid nodule

Thyroid nodule

- A thyroid nodule is a discrete lesion within the thyroid gland that is radiologically distinct from the surrounding thyroid parenchyma.

- Nonpalpable nodules detected on US or other anatomic imaging studies are termed incidentally discovered nodules or "incidentalomas."

- Nonpalpable nodules have the same risk of malignancy as do sonographically confirmed palpable nodules of the same size.

Epidemiology

- The prevalence of thyroid nodules depends on the method of detection.
- By palpation, nodules are identified in approximately 5% to 10% of patients.
- The use of a sensitive imaging modality such as ultrasound (US), however, reveals nodular thyroid disease in as many as 34.2% of patients. (19%–68% of randomly selected individuals)

Thyroid nodule

- About 16 million of individuals in the United States are estimated to have a palpable nodule; up to 219 million have an ultrasound-detectable nodule.

- The main goal should be the identification of nodules that are clinically relevant.

Thyroid nodule

- These include the subgroup harboring a significant cancer (approximately 10%)
- Those causing (or are at risk of causing) compressive symptoms (5%)
- Or thyroid dysfunction (5%).
- Approximately 90% of thyroid nodules are benign and 95% are asymptomatic and remain so during follow-up.

Thyroid nodule

- The reported prevalence is about 65% with ultrasonography
- 15% with CT or MRI
- 1% to 2% with 18fluorodeoxyglucose positron emission tomography (PET).
- Nodules are solitary in about the half of the patients.
- The prevalence of thyroid nodules and the rate of multinodularity increase with age, female sex, and BMI.

[18F]FDG PET scan

- Focal 18FDG-PET uptake in the thyroid is incidentally detected in 1%–2% of patients
- Additional 2% of patients demonstrate diffuse thyroid uptake.

- Importantly, focal 18FDG-PET uptake increases malignancy risk in an affected nodule, and therefore clinical evaluation and FNA of nodules >1 cm is recommended.

- 18FDG-PET positive thyroid nodules <1 cm that do not meet FNA criteria

[18F]FDG PET scan

RECOMMENDATION 5

(A) Focal 18FDG-PET) uptake within a sonographically confirmed thyroid nodule conveys an increased risk of thyroid cancer, and FNA is recommended for those nodules >1 cm.

(Strong recommendation, Moderate-quality evidence)

B) Diffuse 18FDG-PET uptake, in conjunction with sonographic and clinical evidence of chronic lymphocytic thyroiditis, does not require further imaging or FNA.

(Strong recommendation, Moderate-quality evidence)

[18F]FDG PET scan

- A recent meta-analysis confirmed that approximately one in three (35%) 18FDG-PET positive thyroid nodules proved to be cancerous

- In contrast, diffuse thyroid uptake most often represents benign disease corresponding to inflammatory uptake in the setting of Hashimoto’s disease or other diffuse thyroidal illness.

Thyroid nodule

- Nodularity within the thyroid increases linearly with age.
- Thyroid nodules are seen in 12.9% of those younger than 30 years
- 50% to 70% of those older than 70 years have one or more nodules
- The risk is further modified by gender, with women having a 3 to 4 times higher likelihood of nodularity than men.

Thyroid nodule

- With the discovery of a thyroid nodule, a complete history and physical examination focusing on the thyroid gland and adjacent cervical lymph nodes should be performed.

- Pertinent physical findings suggesting possible malignancy include:
- Rapid nodule growth
- Hoarseness, vocal cord paralysis, cervical lymphadenopathy, and fixation of the nodule to surrounding tissue.

Risk factors for malignancy

Risk factors for malignancy Include:

- Childhood irradiation (mainly head and neck and whole body radiation)
- Exposure to ionizing radiation from fallout in childhood or adolescence
- Family history of thyroid cancer or hereditary syndromes that include thyroid cancer (eg, MEN syndrome type 2, familial adenomatous polyposis)
- Rapid nodule growth
- Hoarseness

Table 1 Increased risk of malignancy in thyroid nodule on history and physical exam [1, 3, 13]

- History of childhood head/neck irradiation [113]
- Total body irradiation for bone marrow transplantation [114]
- Exposure to ionizing radiation from fallout in childhood or adolescence [115, 116]
- Family history of PTC, MTC, or thyroid cancer syndrome (e.g., Cowden's syndrome, familial polyposis, Carney complex, multiple endocrine neoplasia [MEN] 2, Werner syndrome) [117]
- Enlarging nodule/rapid nodule growth
- Cervical lymphadenopathy
- Fixed nodule to surrounding tissue
- Vocal cord paralysis/hoarseness

Table 1. Standardized Sonographic Scoring Systems Proposed or Endorsed by Practice Guidelines for Risk-Based Fine-Needle Aspiration Biopsy Guidance for Thyroid Nodules

AACE, ACE, and AME, 2016[22]	ATA, 2015[1]	EU-TIRADS, 2017[31]	ACR TIRADS, 2017[30]
Low-Risk and Benign Thyroid Nodules			
Low-risk definition Risk of malignancy, 1% FNAB >20 mm (selective)[a] Sonographic pattern Cysts (fluid component >80%) Mostly cystic nodules with reverberating artifacts and not associated with suspicious ultrasound signs Isoechoic spongiform nodules, either confluent or with regular halo	Benign definition Risk of malignancy, <1% FNAB is not indicated Sonographic pattern Purely cystic nodules (no solid component)	Benign (EU-TIRADS 2) definition Risk of malignancy, ≈0% FNAB is not indicated Sonographic pattern Pure, anechoic cysts; Entirely spongiform nodules	Benign (TR1) definition Risk of malignancy, 2% FNAB is not indicated Sonographic pattern Spongiform Pure cyst
			Not suspicious (TR2) definition Risk of malignancy, 2% FNAB is not indicated Sonographic pattern Mixed cystic/solid noncalcified nodules with smooth margins and oval shape
	Very low-suspicion definition Risk of malignancy, <3% FNAB ≥20 mm or observation Sonographic pattern Spongiform/partially cystic nodules without any ultrasound features defining low-, intermediate-, or high-suspicion patterns	Low-risk (EU-TIRADS 3) definition Risk of malignancy, 2%-4% FNAB >20 mm Sonographic pattern Oval shape, smooth margins, isoechoic or hyperechoic, without any feature of high risk	Mildly suspicious (TR3) definition Risk of malignancy, 5% FNAB ≥25 mm Sonographic pattern Isoechoic solid or hypoechoic cystic noncalcified nodules with smooth margins and oval shape
	Low suspicion definitions Risk of malignancy, 5%-10% FNAB ≥15 mm Sonographic pattern Isoechoic/hyperechoic solid or partially cystic nodule with eccentric solid area without microcalcifications, irregular margin, extrathyroidal extension, taller than wide shape		

Intermediate or Moderately Suspicious Thyroid Nodules			
Intermediate-risk definition Risk of malignancy, 5%-15% FNAB >20 mm Sonographic pattern Slightly hypoechoic (vs thyroid tissue) or isoechoic nodules, with ovoid-to-round shape, smooth or ill-defined margins May be present Intranodular vascularization Elevated stiffness at elastography Macro or continuous rim calcifications Indeterminate hyperechoic spots	Intermediate-suspicion definition Risk of malignancy, 10%-20% FNAB ≥10 mm Sonographic pattern Hypoechoic solid nodule with smooth margins without microcalcifications, extrathyroidal extension or taller than wide shape	Intermediate-risk (EU-TIRADS 4) definition Risk of malignancy, 6%-17% FNAB >15 mm Sonographic pattern Oval shape, smooth margins, mildly hypoechoic, without any feature of high risk	Moderately suspicious (TR4) definition Risk of malignancy, 5%-20% FNAB >15 mm Sonographic patterns Hypoechoic solid noncalcified nodules with oval shape and either smooth or irregular or lobulated margins Isoechoic solid or mixed noncalcified nodules with either nonparallel orientation (taller than wide), lobulated or irregular margins, or punctate echogenic foci

Table 1. Standardized Sonographic Scoring Systems Proposed or Endorsed by Practice Guidelines for Risk-Based Fine-Needle Aspiration Biopsy Guidance for Thyroid Nodules (continued)

AACE, ACE, and AME, 2016[22]	ATA, 2015[1]	EU-TIRADS, 2017[31]	ACR TIRADS, 2017[30]
High-Risk or Suspicious Thyroid Nodules			
High-risk definition Risk of malignancy, 50%-90%[b] FNAB ≥10 mm (5 mm, selective)[c] Sonographic patterns Nodules with ≥ 1 of the following: Marked hypoechogenicity (vs prethyroid muscles) Spiculated or lobulated margins Microcalcifications Taller-than-wide shape Extrathyroidal growth Pathologic adenopathy	High-suspicion definiton Risk of malignancy, >70%-90% FNAB ≥10 mm Sonographic pattern Solid hypoechoic nodule or solid hypoechoic component of partially cystic nodule with ≥1 of the following: Irregular margins (infiltrative, microlobulated) Microcalcifications Taller than wide shape Rim calcifications with small extrusive soft tissue Extrathyroidal extension	High-risk (EU-TIRADS 5) definition Risk of malignancy, 26%-87% FNAB >10 mm Sonographic pattern Nodules with ≥ 1 of the following: Nonoval shape Irregular margins Microcalcifications Marked hypoechogenicity	Suspicious (TR5) definition Risk of malignancy, ≥20% FNAB >10 mm Sonographic pattern Hypoechoic solid nodule with any of the following Nonparallel orientation (taller than wide) Extrathyroidal extension Punctate echogenic foci Isoechoic solid nodule with irregular or lobulated margins and either peripheral rim calcifications or punctate echogenic foci

Abbreviations. AACE/ACE/AME, American Association of Clinical Endocrinologists, American College of Endocrinology, and Associazione Medici Endocrinologi; ACR, American College of Radiologists; ATA, American Thyroid Association; EU-TIRADS, European Thyroid Imaging Reporting and Data System; FNAB, fine-needle aspiration biopsy; TR, American College of Radiologists Thyroid Imaging Reporting and Data System.

[a] Growing nodule, high-risk history, before surgery or local therapies.

[b] In accordance with the presence of 1 or more suspicious findings.

[c] An FNAB is recommended for smaller nodules that are subcapsular location near the recurrent nerve or trachea; suspicious lymph nodes or extrathyroid spread; personal or family history of thyroid cancer; history of head and neck irradiation; coexistent suspicious clinical findings. An FNAB indicates the size above which a FNAB cytology is recommended.

[A3] What is the **appropriate laboratory and imaging** evaluation for patients with clinically or incidentally discovered thyroid nodules?

RECOMMENDATION 2

- (A) Serum TSH should be measured during the initial evaluation of a patient with a thyroid nodule. (Strong recommendation, Moderate-quality evidence)

- (B) If the serum TSH is subnormal, a radionuclide (preferably 123I) thyroid scan should be performed. (Strong recommendation, Moderate-quality evidence)

[A3] What is the **appropriate laboratory and imaging** evaluation for patients with clinically or incidentally discovered thyroid nodules?

RECOMMENDATION 2

- (C) If the serum TSH is normal or elevated, a radionuclide scan should not be performed as the initial imaging evaluation.

(Strong recommendation, Moderate-quality evidence)

Thyroid nodule

- With the discovery of a thyroid nodule >1 cm in any diameter, a serum TSH level should be obtained.
- If the serum TSH is subnormal, a radionuclide thyroid scan should be obtained to document whether the nodule is hyperfunctioning (hot), warm or cold.

- Since hyperfunctioning nodules rarely harbor malignancy, if one is found that corresponds to the nodule in question, no cytologic evaluation is necessary

Thyroid nodule

- Pertinent historical factors predicting malignancy include:
- History of childhood head and neck radiation therapy
- total body radiation for bone marrow transplantation (42)
- exposure to ionizing radiation from fallout in childhood or adolescence (43)
- familial thyroid carcinoma, or thyroid cancer syndrome (e.g., PTEN hamartoma tumor syndrome [Cowden’s disease], FAP, Carney complex, Werner syndrome/progeria
- MEN 2, a risk for medullary thyroid cancer [MTC]) in a first degree relative,

[A5] Serum thyroglobulin measurement

RECOMMENDATION 3

- Routine measurement of serum thyroglobulin (Tg) for initial evaluation of thyroid nodules is not recommended.

(Strong recommendation, Moderate-quality evidence)

- Serum Tg levels can be elevated in most thyroid diseases and are an insensitive and nonspecific test for thyroid cancer

[A6] Serum calcitonin measurement

RECOMMENDATION 4

- The panel cannot recommend either for or against routine measurement of serum calcitonin in patients with thyroid nodules.

(No recommendation, Insufficient evidence)

[A7] [18F]FDG PET scan

RECOMMENDATION 5

(A) Focal 18FDG-PET) uptake within a sonographically confirmed thyroid nodule conveys an increased risk of thyroid cancer, and FNA is recommended for those nodules >1 cm.

(Strong recommendation, Moderate-quality evidence)

B) Diffuse 18FDG-PET uptake, in conjunction with sonographic and clinical evidence of chronic lymphocytic thyroiditis, does not require further imaging or FNA.

(Strong recommendation, Moderate-quality evidence)

[18F]FDG PET scan

- Focal 18FDG-PET uptake in the thyroid is incidentally detected in 1%–2% of patients
- additional 2% of patients demonstrate diffuse thyroid uptake (60–62).

- Importantly, focal 18FDG-PET uptake increases malignancy risk in an affected nodule, and therefore clinical evaluation and FNA of nodules >1 cm is recommended.

- 18FDG-PET positive thyroid nodules <1 cm that do not meet FNA criteria

[18F]FDG PET scan

- A recent meta-analysis confirmed that approximately one in three (35%) 18FDG-PET positive thyroid nodules proved to be cancerous

- In contrast, diffuse thyroid uptake most often represents benign disease corresponding to inflammatory uptake in the setting of Hashimoto’s disease or other diffuse thyroidal illness.

[A8] Thyroid sonography

RECOMMENDATION 6

- Thyroid sonography with survey of the cervical lymph nodes should be performed in all patients with known or suspected thyroid nodules. (Strong recommendation, High-quality evidence)

[A9] US for FNA decision-making

RECOMMENDATION 7

- FNA is the procedure of choice in the evaluation of thyroid nodules, when clinically indicated. (Strong recommendation, High-quality evidence)

- FNA is the most accurate and cost-effective method for evaluating thyroid nodules.

[A10] Recommendations for diagnostic FNA of a thyroid nodule based on sonographic pattern

RECOMMENDATION 8

I = Thyroid nodule diagnostic FNA is recommended for:

- (A) Nodules >1 cm in greatest dimension with high suspicion sonographic pattern.

(Strong recommendation, Moderate-quality evidence)

- (B) Nodules >1 cm in greatest dimension with intermediate suspicion sonographic pattern. (Strong recommendation, Low-quality evidence)

- (C) Nodules >1.5 cm in greatest dimension with low suspicion sonographic pattern. (Weak recommendation, Low-quality evidence)

Recommendations for diagnostic FNA of a thyroid nodule based on sonographic pattern

II. Thyroid nodule diagnostic FNA may be considered for:

- (D) Nodules >2 cm in greatest dimension with very low suspicion sonographic pattern (e.g., spongiform). Observation without FNA is also a reasonable option.

(Weak recommendation, Moderate-quality evidence)

Recommendations for diagnostic FNA of a thyroid nodule based on sonographic pattern

- III. Thyroid nodule diagnostic FNA is not required for

- (E) Nodules that do not meet the above criteria.

(Strong recommendation, Moderate-quality evidence)

- (F) Nodules that are purely cystic.

(Strong recommendation, Moderate-quality evidence)

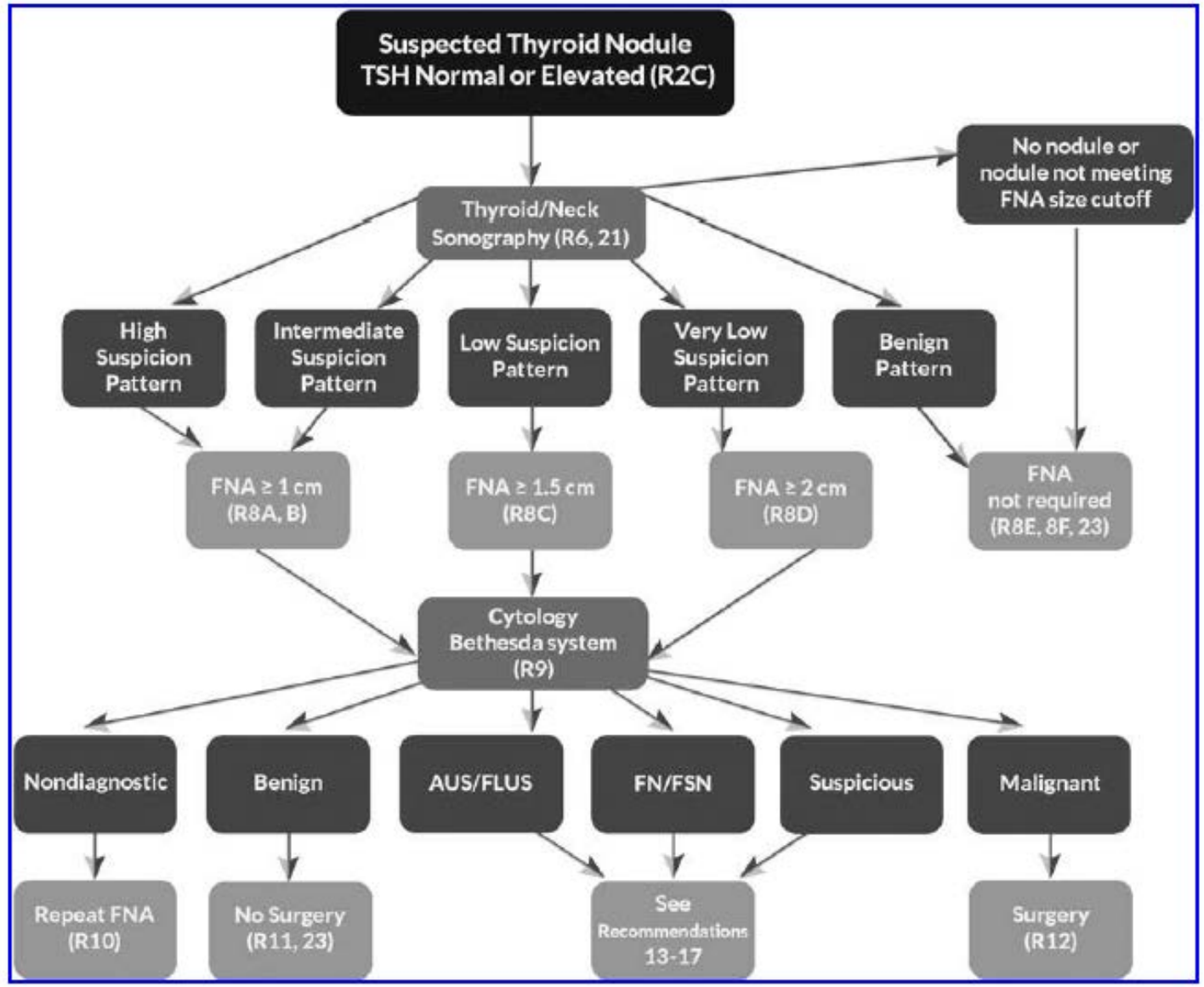


FIG. 1. Algorithm for evaluation and management of patients with thyroid nodules based on US pattern and FNA cytology. R, recommendation in text.

Thyroid sonography

Table 1
Features of sonographic examination report

Thyroid Gland Features	Nodule Features	Lymph Node Features
Size of each lobe	Size	Size
Echogenicity	Location	Shape
Texture (smooth/heterogeneous)	Echogenicity	Calcifications/cystic change
Vascularity	Composition	Location
Tracheal deviation	Echogenic foci	Vascular pattern
Isthmus thickness	Margins	Echogenicity
	Vascular pattern	

Table 2
ACR-TIRADS nodule features and associated points for each characteristic

Composition		Echogenicity		Shape		Margin		Echogenic Foci	
Cystic	0	Anechoic	0	Wider than tall	0	Smooth	0	None	0
Spongiform	0	Hyper/isoechoic	1	Taller than wide	3	Ill-defined	0	Comet-tails	0
Mixed	1	Hypoechoic	2			Lobulated/irregular	2	Macrocalcifications	1
Solid	2	Markedly hypoechoic	3			Extrathyroidal extension	3	Peripheral/rim	2
								Punctate	3

Table 3
ACR-TIRADS scores

Score	0	2	3	4–6	7
TIRADS class	TR1	TR2	TR3	TR4	TR5
Clinical description	Benign	Not Suspicious	Mildly Suspicious	Moderately Suspicious	Highly Suspicious

Table 4
Comparison of management recommendations in stratification systems of the ATA

Categorization	Description	FNA Size Threshold	Surveillance Interval if Benign Cytology
ATA			
Benign	Anechoic cyst	Not recommended	Not recommended
Very Low	Complex; spongiform	≥2 cm	≥24 mo or clinical surveillance
Low	Complex or solid hyper/isoechoic	≥1.5 cm	12–24 mo
Intermediate	Solid hypoechoic	≥1 cm	12–24 mo
High	Hypoechoic with suspicious feature	≥1 cm	Repeat FNA and US within 12 mo
ACR-TIRADS			
0 Benign	0 points (see Table 2)	Not recommended	
2 Not Suspicious	2 points (see Table 2)	Not recommended	
3 Mildly Suspicious	3 points (see Table 2)	FNA ≥2.5 cm Follow ≥1.5 cm	At 1, 3, and 5 y
4 Moderately Suspicious	4–6 points (see Table 2)	FNA ≥1.5 cm Follow ≥1.0 cm	At 1, 2, 3, and 5 y
5 Highly suspicious	≥7points (see Table 2)	FNA ≥1. 0 cm Follow ≥0.5 cm	Annually for 5 y

High suspicion (malignancy risk >70%–90%)

a solid hypoechoic nodule or a solid hypoechoic component in a partially cystic nodule with one or more of the following features:

Irregular margins (specifically defined as infiltrative, microlobulated, or spiculated)

Microcalcifications

Taller than wide shape

Disrupted rim calcifications with small extrusive hypoechoic soft tissue component

Evidence of extrathyroidal extension (Fig. 2, Table 6)

High suspicion (malignancy risk >70%–90%)

- A nodule demonstrating this US pattern is highly likely to be a PTC.

- Nodules with the high suspicion pattern and measuring >1 cm should undergo diagnostic fine-needle biopsy to refute or confirm malignancy.

High suspicion (malignancy risk >70%–90%)

- However, in the absence of evidence of extrathyroidal extension, metastatic cervical lymph nodes, or distant metastases, micropapillary thyroid cancers (<1 cm) often have an indolent course, but this may depend upon patient age (95).

High suspicion (malignancy risk >70%–90%)

- Thus although a sonographically suspicious subcentimeter thyroid nodule without evidence of extrathyroidal extension or sonographically suspicious lymph nodes may be observed with close sonographic follow-up of the nodule and cervical lymph nodes, rather than pursuing immediate FNA, patient age and preference may modify decision-making (95).

Intermediate suspicion (malignancy risk 10%–20%)

Intermediate suspicion of malignancy is attached to a hypoechoic solid nodule with a smooth regular margin, but without microcalcifications, extrathyroidal extension, or taller than wide shape (Fig. 2, Table 6).

- This appearance has the highest sensitivity (60%–80%) for PTC, but a lower specificity than the preceding high suspicion pattern, and fine-needle biopsy should be considered for these nodules >1 cm to refute malignancy

Low suspicion (malignancy risk 5%–10%)

- Isoechoic or hyperechoic solid nodule, or partially cystic nodule with eccentric uniformly solid areas without microcalcifications, irregular margin or extrathyroidal extension, or taller than wide shape prompts low suspicion for malignancy (Fig. 2, Table 6).

Low suspicion (malignancy risk 5%–10%)

- Only about 15%–20% of thyroid cancers are iso- or hyperechoic on US, and these are generally the follicular variant of PTC or FTCs (71).
- Fewer than 20% of these nodules are partially cystic.
- Therefore, these appearances are associated with a lower probability of malignancy and observation may be warranted until the size is >1.5 cm.

Very low suspicion (<3%)

- Spongiform or partially cystic nodules without any of the sonographic features described in the low, intermediate, or high suspicion patterns have a low risk of malignancy (<3%).
- If FNA is performed, the nodule should be at least 2 cm.

- Observation without FNA may also be considered for nodules >2 cm (Fig. 2, Table 6).

Benign (<1%)

- Purely cystic nodules are very unlikely to be malignant, and fine-needle biopsy is not indicated for diagnostic purposes (Fig. 2, Table 6).

- Aspiration with or without ethanol ablation may be considered as a therapeutic intervention if a cyst is large and symptomatic; cytology should be performed if aspiration is done.

Ultrasound cervical LN

- Sonographic evaluation of the anterior cervical lymph node compartments (central and lateral) should be performed whenever thyroid nodules are detected.

- If US detects cervical lymph nodes that are sonographically suspicious for thyroid cancer, FNA of the suspicious lymph node should be performed for cytology and washout for Tg measurement if indicated.

Ultrasound features of LN

TABLE 7. ULTRASOUND FEATURES OF LYMPH NODES PREDICTIVE OF MALIGNANT INVOLVEMENT[a]

Sign	*Reported sensitivity, %*	*Reported specificity, %*
Microcalcifications	5–69	93–100
Cystic aspect	10–34	91–100
Peripheral vascularity	40–86	57–93
Hyperechogenicity	30–87	43–95
Round shape	37	70

[a]Adapted with permission from the European Thyroid Association guidelines for cervical ultrasound (20).

Management recommendation

ACE			
Low	Cystic, spongiform, complex with colloid inclusions	≥2 cm and increasing in size or other clinical risk factor	≥12 mo or clinical surveillance
Intermediate	Solid or complex without suspicious features	≥2 cm	≥12 mo or clinical surveillance
High	Markedly hypoechoic or other suspicious features	≥0.5–1 cm	Repeat FNA

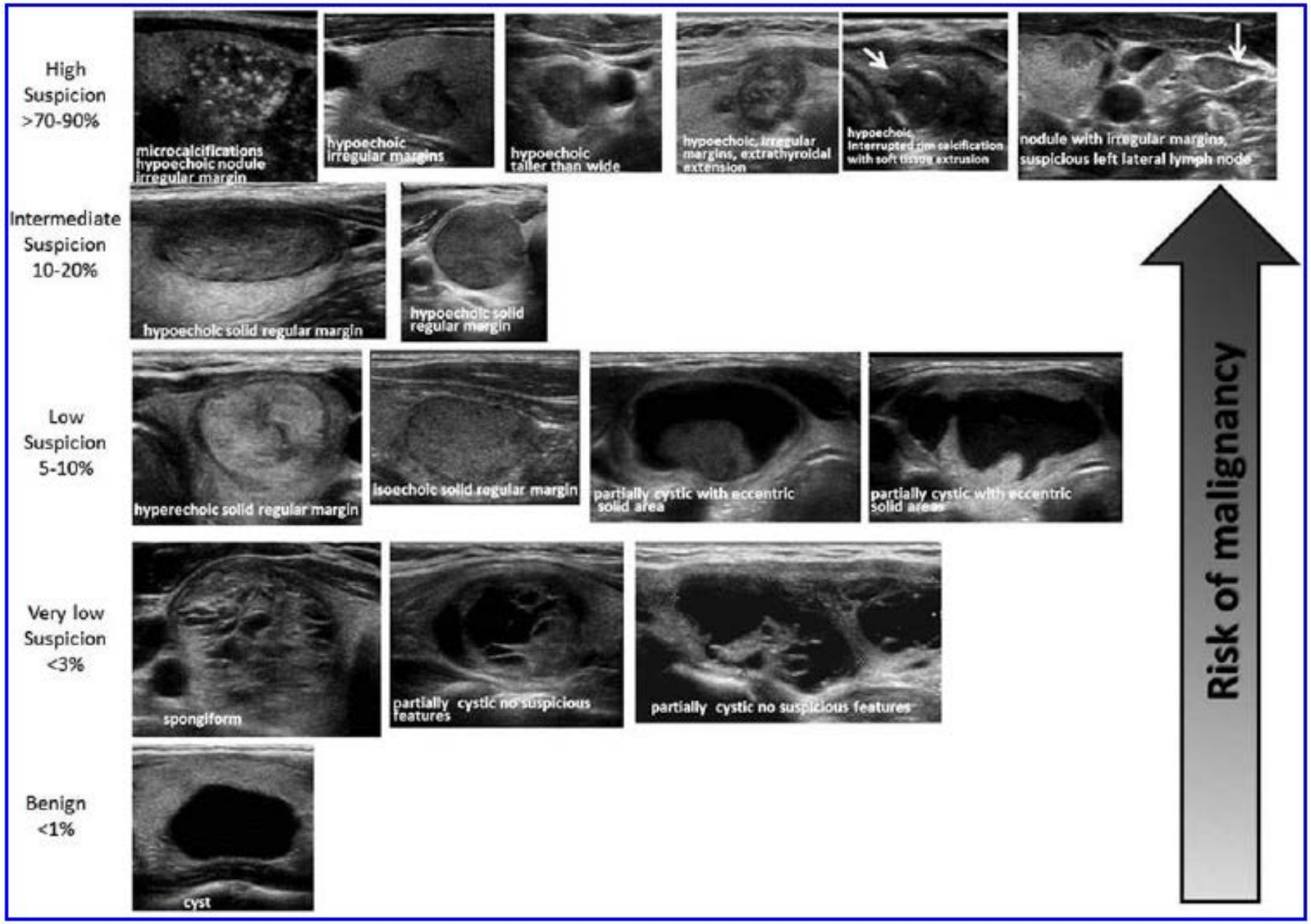
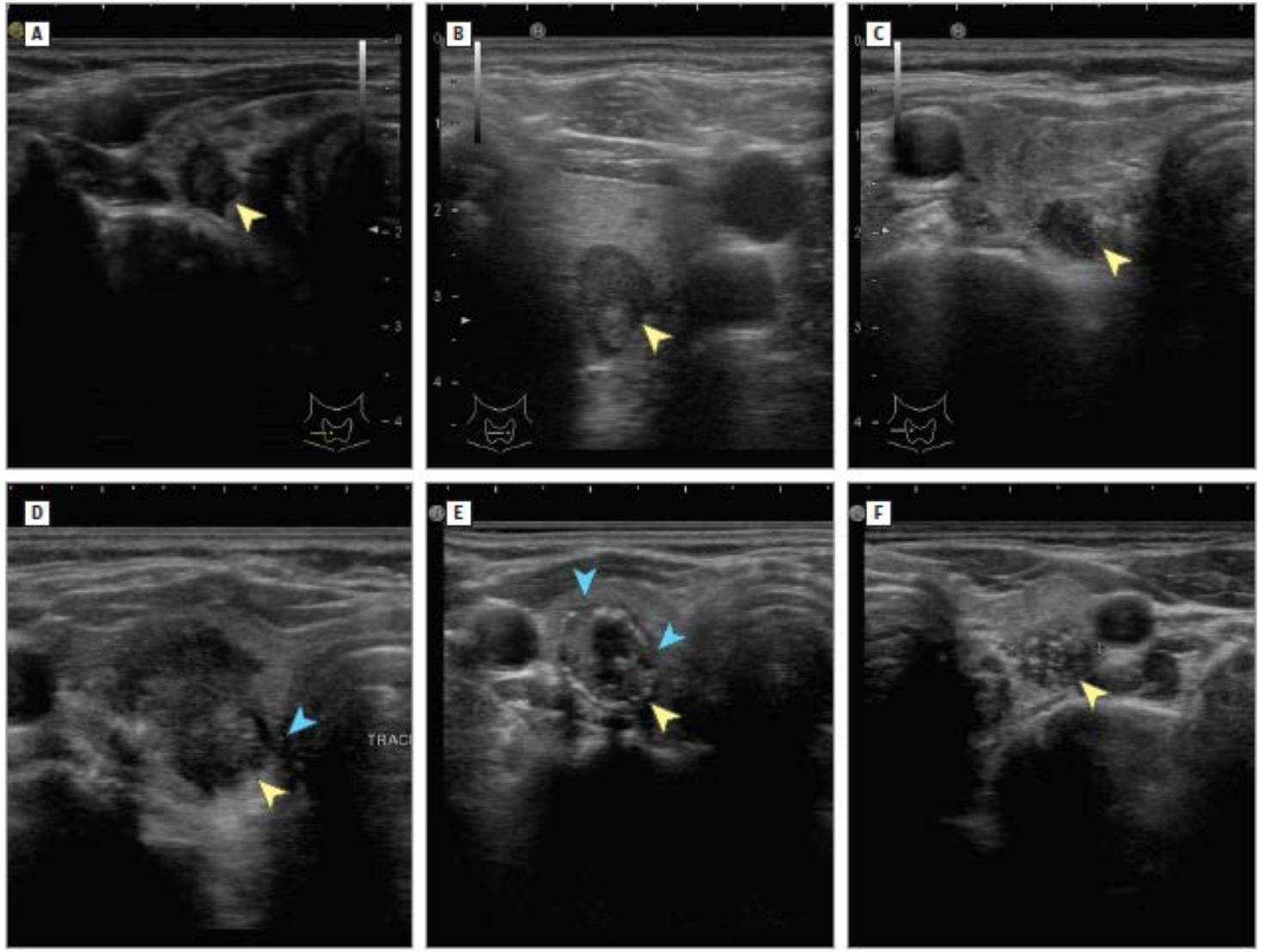


FIG. 2. ATA nodule sonographic patterns and risk of malignancy.

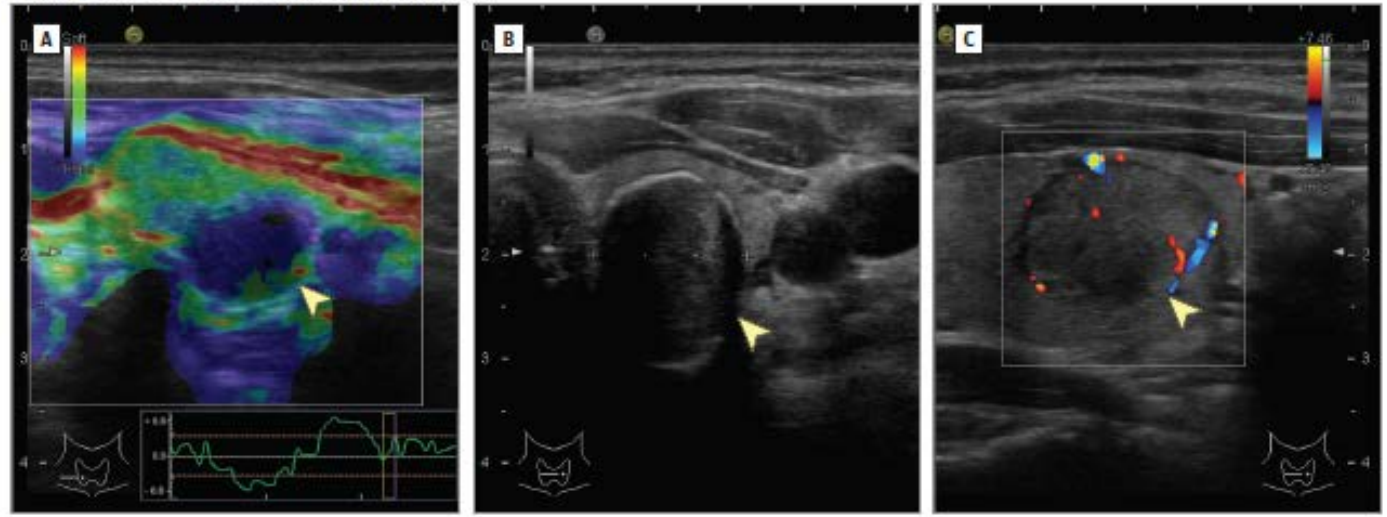
Figure 1. Ultrasonographic Features of Thyroid Nodules Suspicious for Malignancy



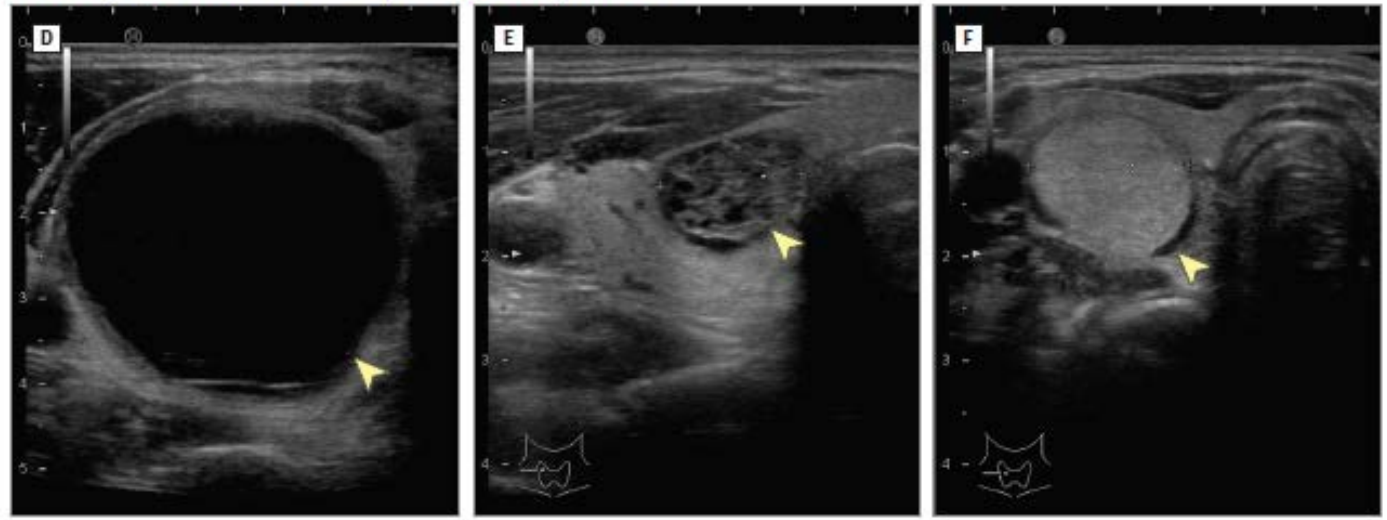
A, Markedly hypoechoic nodule (similar echogenicity as the surrounding strap muscles) with irregular margins. B, Taller-than-wide hypoechoic nodule. C, Markedly hypoechoic nodule with regular margins. D, Hypoechoic nodule with infiltrative margins and suspicious extrathyroidal extension (indicated by a blue arrowhead). E, Multiple interruptions in calcific rim with evidence of extrusive tissue (indicated by blue arrowheads). Echogenicity is difficult to interpret because of acoustic shadowing of the calcific rim). F, hypoechoic solid nodule with microcalcifications and irregular margins. The yellow arrowheads indicate the thyroid nodule in each panel. The gray scale graphically represents the shades of gray that can be provided by the ultrasound equipment.

Figure 2. Imaging Features of Indeterminate and Low Suspicion Thyroid Nodules

Imaging features of indeterminate thyroid nodules



Ultrasonographic features of low or very low suspicion thyroid nodules



A, Elevated stiffness at elastography (red indicates soft tissues; blue, hard tissues; and green, intermediate values of stiffness). B, Complete rim calcification. C, Slightly hypoechoic nodule with intranodular vascularization. Flow velocity is converted into a color scale. Flow toward the transducer is represented in red; away from the transducer is depicted in blue. D, pure cyst. E, Spongiform nodule with more than 50% of the nodule volume composed of microcystic spaces. F, solid hyperechoic nodule. The arrowheads indicate the thyroid nodule in each panel. The gray scale graphically represents the shades of gray that can be provided by the ultrasound equipment.

TABLE 6. SONOGRAPHIC PATTERNS, ESTIMATED RISK OF MALIGNANCY, AND FINE-NEEDLE ASPIRATION GUIDANCE FOR THYROID NODULES

Sonographic pattern	*US features*	*Estimated risk of malignancy, %*	*FNA size cutoff (largest dimension)*
High suspicion	Solid hypoechoic nodule or solid hypoechoic component of a partially cystic nodule ***with*** one 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[a]	Recommend FNA 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*** microcalcification, irregular margin or ETE, or taller than wide shape.	5–10	Recommend FNA at ≥1.5 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 FNA at ≥2 cm Observation without FNA is also a reasonable option
Benign	Purely cystic nodules (no solid component)	<1	No biopsy[b]

US-guided FNA is recommended for cervical lymph nodes that are sonographically suspicious for thyroid cancer (see Table 7).

[a]The estimate is derived from high volume centers, the overall risk of malignancy may be lower given the interobserver variability in sonography.

[b]Aspiration of the cyst may be considered for symptomatic or cosmetic drainage.

ETE, extrathyroidal extension.

[A11] What is the role of FNA, cytology interpretation, and molecular testing in patients with thyroid nodules?

RECOMMENDATION 9

- Thyroid nodule FNA cytology should be reported using diagnostic groups outlined in the Bethesda System for Reporting Thyroid Cytopathology.

(Strong recommendation, Moderate-quality evidence)

TABLE 1. THE 2017 BETHESDA SYSTEM FOR REPORTING THYROID CYTOPATHOLOGY: RECOMMENDED DIAGNOSTIC CATEGORIES

I. NONDIAGNOSTIC OR UNSATISFACTORY
Cyst fluid only
Virtually acellular specimen
Other (obscuring blood, clotting artifact, etc.)
II. BENIGN
Consistent with a benign follicular nodule (includes adenomatoid nodule, colloid nodule, etc.)
Consistent with lymphocytic (Hashimoto) thyroiditis in the proper clinical context
Consistent with granulomatous (subacute) thyroiditis
Other
III. ATYPIA OF UNDETERMINED SIGNIFICANCE *or* FOLLICULAR LESION OF UNDETERMINED SIGNIFICANCE
IV. FOLLICULAR NEOPLASM *or* SUSPICIOUS FOR A FOLLICULAR NEOPLASM
Specify if Hürthle cell (oncocytic) type
V. SUSPICIOUS FOR MALIGNANCY
Suspicious for papillary carcinoma
Suspicious for medullary carcinoma
Suspicious for metastatic carcinoma
Suspicious for lymphoma
Other
VI. MALIGNANT
Papillary thyroid carcinoma
Poorly differentiated carcinoma
Medullary thyroid carcinoma
Undifferentiated (anaplastic) carcinoma
Squamous-cell carcinoma
Carcinoma with mixed features (specify)
Metastatic carcinoma
Non-Hodgkin lymphoma
Other

TABLE 2. THE 2017 BETHESDA SYSTEM FOR REPORTING THYROID CYTOPATHOLOGY: IMPLIED RISK OF MALIGNANCY AND RECOMMENDED CLINICAL MANAGEMENT

Diagnostic category	*Risk of malignancy if NIFTP ≠ CA (%)*	*Risk of malignancy if NIFTP = CA (%)*	*Usual management*[a]
Nondiagnostic or unsatisfactory	5–10	5–10	Repeat FNA with ultrasound guidance
Benign	0–3	0–3	Clinical and sonographic follow-up
Atypia of undetermined significance or follicular lesion of undetermined significance	6–18	~10–30	Repeat FNA, molecular testing, or lobectomy
Follicular neoplasm or suspicious for a follicular neoplasm	10–40	25–40	Molecular testing, lobectomy
Suspicious for malignancy	45–60	50–75	Near-total thyroidectomy or lobectomy[b,c]
Malignant	94–96	97–99	Near-total thyroidectomy or lobectomy[c]

Adapted with permision from Ali and Cibas (7).

[a]Actual management may depend on other factors (e.g., clinical, sonographic) besides the FNA interpretation.

[b]Some studies have recommended molecular analysis to assess the type of surgical procedure (lobectomy vs. total thyroidectomy).

[c]In the case of ''suspicious for metastatic tumor'' or a ''malignant'' interpretation indicating metastatic tumor rather than a primary thyroid malignancy, surgery may not be indicated.

NIFTP, noninvasive follicular thyroid neoplasm with papillary-like nuclear features; CA, carcinoma; FNA, fine-needle aspiration.

[A12] Nondiagnostic cytology

RECOMMENDATION 10

- (A) For a nodule with an initial nondiagnostic cytology result, FNA should be repeated with US guidance and, if available, on-site cytologic evaluation

(Strong recommendation, Moderate-quality evidence)

- (B) Repeatedly nondiagnostic nodules without a high suspicion sonographic pattern require close observation or surgical excision for histopathologic diagnosis

(Weak recommendation, Low-quality evidence)

[A12] Nondiagnostic cytology

RECOMMENDATION 10

- (C) Surgery should be considered for histopathologic diagnosis if the cytologically nondiagnostic nodule has
- a high suspicion sonographic pattern
- growth of the nodule (>20% in two dimensions) is detected during US surveillance
- clinical risk factors for malignancy are present

(Weak recommendation, Low-quality evidence)

[A12] Nondiagnostic cytology

- Of 104 nodules with two nondiagnostic cytology results, thyroid cancer was found in 25% of those with microcalcifications, irregular margins, a taller than wide shape, or hypoechogenicity, but in only 4% lacking these features (118).

[A13] Benign cytology

RECOMMENDATION 11

- If the nodule is benign on cytology, further immediate diagnostic studies or treatment are not required

(Strong recommendation, High-quality evidence)

[A14] Malignant cytology

RECOMMENDATION 12

- If a cytology result is diagnostic for primary thyroid malignancy, surgery is generally recommended.

(Strong recommendation, Moderate-quality evidence)

Table 2. The Bethesda System for Reporting Thyroid Cytopathology: Implied Risk of Malignancy and Recommended Clinical Management

Diagnostic Category	Risk of Malignancy, %	Usual Management[a]
Category 1: Nondiagnostic or Unsatisfactory		
Cyst fluid only Virtually acellular specimen Obscuring blood, artifacts	0-5[b]	Repeat FNAB with ultrasound guidance
Category 2: Benign		
Benign follicular nodule (eg, adenomatoid nodule, colloid nodule) Chronic lymphocytic (Hashimoto) thyroiditis Granulomatous (subacute) thyroiditis	0-3[c]	Clinical and sonographic follow-up[c]
Category 3: Atypia of Undetermined significance or Follicular Lesion of Undetermined Significance		
Focal nuclear atypia Predominance of Hurthle cells Microfollicular pattern in a hypocellular specimen	≈10-30[d]	Repeat FNAB, molecular testing, or lobectomy

Category 4: Follicular Neoplasm or Suspicious for a Follicular Neoplasm[f]		
Crowded and overlapping follicular cells some or most of which are arranged as microfollicles	25-40[e]	Molecular testing, lobectomy
Category 5: Suspicious for Malignancy		
Suspicious for papillary thyroid carcinoma Suspicious for medullary thyroid carcinoma Suspicious for metastatic carcinoma Suspicious for lymphoma	50-75	Near total thyroidectomy or lobectomy[g,h]
Category 6: Malignant		
Papillary thyroid carcinoma Poorly differentiated carcinoma Medullary thyroid carcinoma Undifferentiated (anaplastic) carcinoma Squamous cell carcinoma Carcinoma with mixed features (to be described)	97-99	Near total thyroidectomy[h,I]

Abbreviation: FNAB, fine-needle aspiration biopsy.

[a] Actual management may depend on other factors (eg, clinical, sonographic) besides the FNA interpretation.

[b] The risk of malignancy varies with the type or structure of the nodule (ie, solid vs complex vs ≥50% cystic). Nondiagnostic aspirates from solid nodules are associated with a higher risk of malignancy vs those showing cystic change of 50% or more and low-risk ultrasonographic features.

[c] Estimate extrapolated from studies showing correlation between biopsied nodule and surgical pathology follow-up.[35-38] See Figure 3 for suggested timing.

[d] Estimates extrapolated from histopathologic data from large case cohorts (including repeat atypical FNAs) and meta-analysis of the post-2007 literature.[35,39-42]

[e] Estimates extrapolated from histopathologic data from large case cohorts and meta-analysis of the post-2007 literature.[35,39-44]

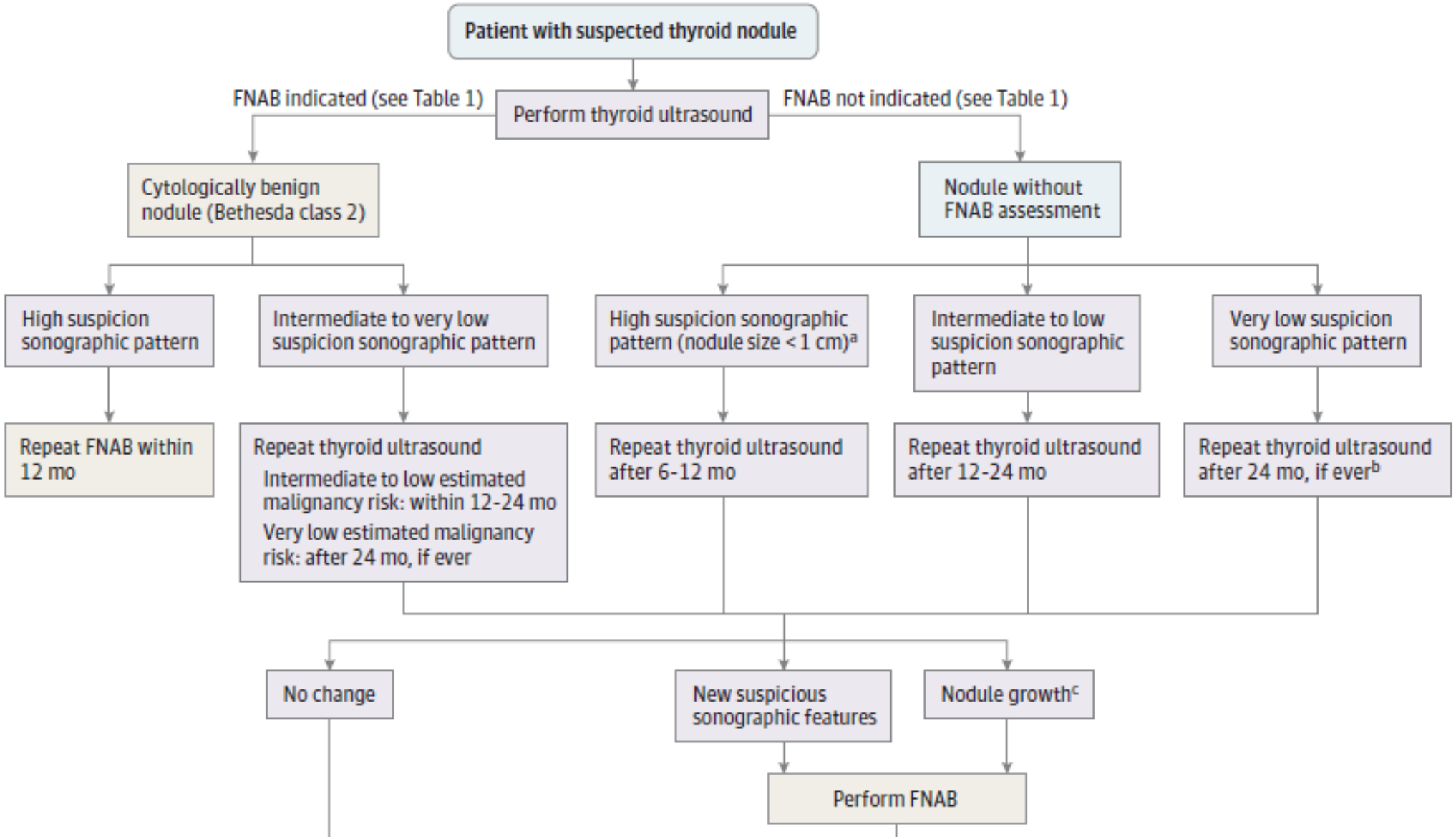
[f] Includes cases of follicular neoplasm with oncocytic features (Hürthle cell neoplasm).

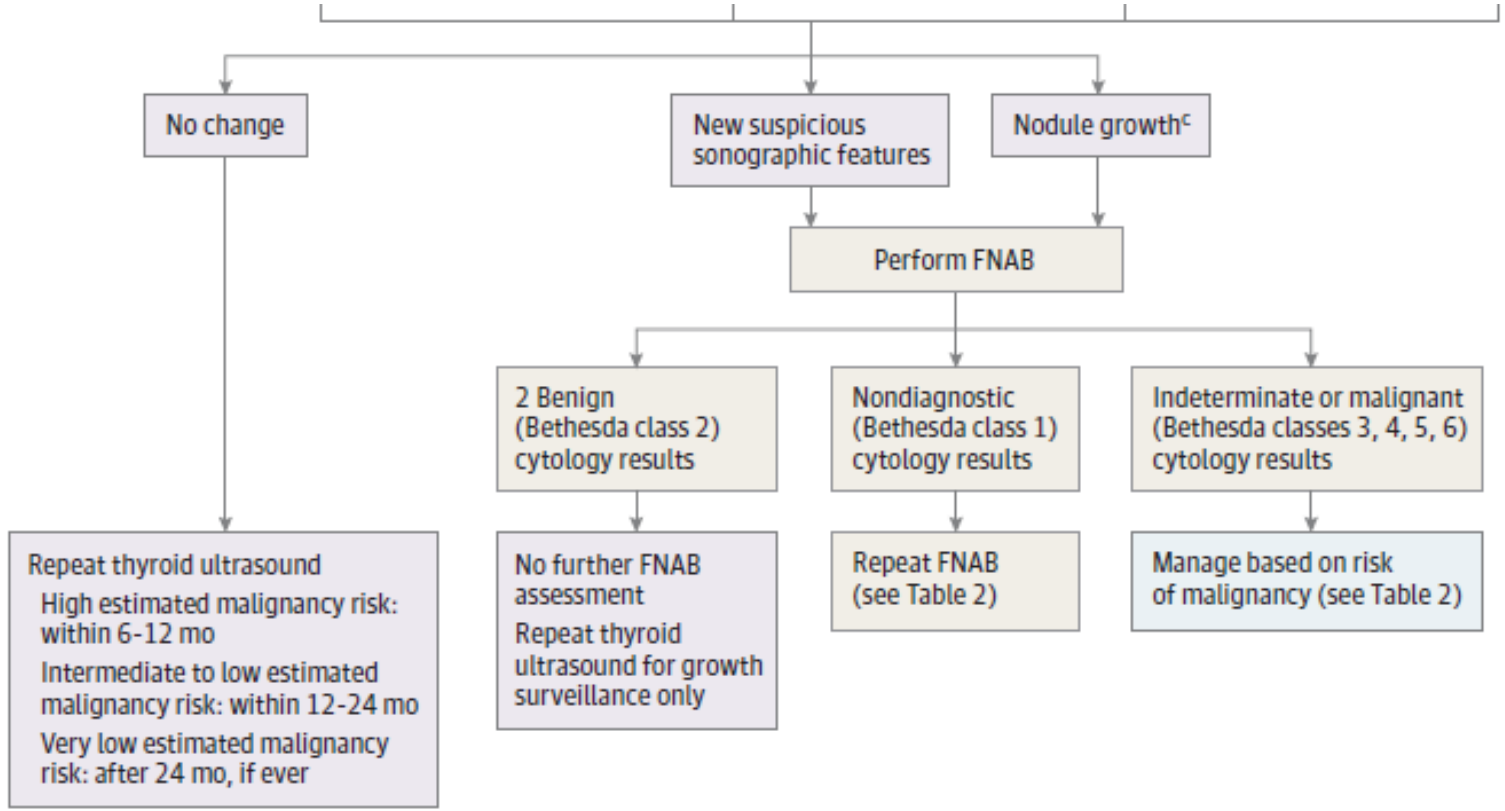
[g] Some studies have recommended molecular analysis to assess the type of surgical procedure (lobectomy vs total thyroidectomy).

[h] In the case of "suspicious for metastatic tumor" or a malignant interpretation indicating metastatic tumor rather than a primary thyroid malignancy, surgery may not be indicated.

[I] Lobectomy is appropriate for most papillary thyroid cancers smaller than 4 cm, without other features such as gross extrathyroidal extension or clinical or radiological lymphadenopathy.

Figure 3. Algorithm for the Follow-up of Cytologically Benign Thyroid Nodules or Nodules Without Indication for Fine-Needle Aspiration Cytology





Sonographic suspicion in this Figure is graded according to the American Thyroid Association Guidelines. FNAB indicates fine-needle aspiration biopsy.

[a] Subcentimeter thyroid nodules harboring high-suspicion sonographic features and not requiring routine biopsy include those nodules without evidence of extrathyroidal extension or sonographically suspicious lymph nodes. Subcapsular location near the recurrent nerve or trachea, patient age (<40 years old being at higher risk) and preference, a strong family history of thyroid cancer or known syndromes associated with thyroid cancer, or a history of therapeutic head and neck or whole body radiation exposure as children may drive decision making toward performing an FNAB.

[b] Nodules smaller than 1 cm with a very low-suspicion pattern do not require routine sonographic follow-up, while such nodules larger than 1 cm should be followed up at more than 24 months intervals, if ever.

[c] The minimal clinically significant change in nodule size should be a 20% increase in at least 2 diameters with a minimum increase of 2 mm, which corresponds to an increase in nodule volume of more than 50%. Compared with a slower growth rate, nodule growth of more than 2 mm a year vs slower growth rate predicts malignancy (relative risk, 2.5; 95% CI, 1.6-3.1; $P < .001$).[71] If compressive symptoms appear following thyroid nodule growth, consider surgery.

Molecular Testing

- Molecular testing of fine-needle aspiration biopsy specimens has gained acceptance in the United States as a popular and potentially practice-changing approach to diagnosing indeterminate thyroid nodules

Molecular Testing

- Mutations occur principally in genes coding for proteins in the mitogen-activated protein kinase (MAPK or MAP kinase) pathway that regulates cellular proliferation and differentiation.

- A mutation in the *BRAF* gene (V600E) is found in approximately 40% of papillary thyroid cancers, as well as in some poorly differentiated (33%) and anaplastic cancers (45%) that likely arise from papillary cancers.54

Molecular Testing

- **Mutations in the *RAS* gene family** are found in some papillary cancers (13%, generally the encapsulated follicular variant)
- follicular thyroid cancers (40%-50%)
- benign follicular adenomas (20%-40%)
- As well as in NIFTP (30%).

Molecular Testing

- Fusion genes, hybrid genes formed from 2 previously separate genes—in which the *RET* gene that codes for a cell surface receptor protein not normally expressed by thyroid follicular cells is fused with a second unrelated gene, called a *RET/PTC* oncogene—has been associated with radiation-related papillary thyroid cancers.

Molecular Testing

- Another fusion gene between the gene coding for the thyroid transcription factor *PAX8* and the peroxisome proliferator-activated receptor, gamma isoform (*PPARG*) gene (*PAX8/PPARG*) is seen in some follicular thyroid cancers (30%-35%), the follicular variant of papillary thyroid cancer (38%), and in some follicular adenomas (2%-13%).

Molecular Testing

- Mutations in the telomerase reverse transcriptase (*TERT*) and *TP53* tumor suppressor genes have also been observed in some thyroid cancers.

- *TERT* has been reported in less than 10% of papillary thyroid cancer and more than 70% of anaplastic thyroid cancer

- *TP53*, in less than 1% of papillary thyroid cancer and more than 70%of anaplastic thyroid cancer.53

Molecular Testing

- The 2 most common molecular testing strategies are mutational analysis and gene expression analysis, in which genetic information can be derived from the same material obtained in the original fine-needle aspiration biopsy sample.

- Mutational analysis involves isolating DNA from thyroid follicular cells in the specimen and performing gene sequencing, focusing on possible mutations in *BRAF*, *RAS*, *TERT*, *TP53*, and other relevant genes, as well for the presence of fusion genes.

Molecular Testing

- Such mutational testing has been termed a *rule in test* because if a *BRAF*, *TERT*, or *TP53* mutation is found or if a fusion gene is detected, thyroid cancer is almost always present.

- However, while mutations in *RAS* genes (*HRAS*, *KRAS*, *NRAS*) are present in thyroid cancers, they are also present in nonmalignant thyroid neoplasms and in NIFTP, and are therefore less specific

Molecular Testing

- Furthermore, if no mutations are found, a thyroid malignancy with a mutation that was not assessed could still be present (≈ 4%); therefore, mutational testing may lead to both false-negative and false-positive results, especially if *RAS* mutations are found.

Molecular Testing

- In a single-institution study involving 239 patients with Bethesda category 3 or 4 cytology, the mutational testing strategy (ThyroSeq v2) yielded a negative predictive value when a mutation was not found of about 96% and a positive predictive value of approximately 80%.57

- In a second single-institution study involving 182 patients with 190 Bethesda category 3 and 4 cytologies, the negative predictive value was 91% (95% CI, 82%-97%) and the positive predictive value was 42% (95% CI, 25%-61%).

Molecular Testing

- *BRAF*- and *RAS*-mutation status may provide information beyond diagnosis:
- *BRAF*-positive malignant nodules are frequently present in malignant or suspicious Bethesda cytology categories and frequently show suspicious sonographic and advanced histological features,

- while *RAS*-positive malignancies are more difficult to identify by sonography, more commonly reported in lower risk, indeterminate cytology categories, and usually have an indolent behavior.59

Molecular Testing

- The second type of molecular testing, gene expression analysis or gene expression classifier (GEC), uses a proprietary algorithm to analyze the expression of specific genes in a 142-gene panel.
- Nodules are classified as benign or suspicious rather than as malignant.
- The test is designed to identify nodules that do not require surgery. In the original multi-institutional validation study, a benign Afirma test had a negative predictive value of approximately 95%

Molecular Testing

- In a pooled analysis of 12 studies involving 1303 nodules, the negative predictive value was 92% (95% CI, 87%- 96%) and the malignancy prevalence of 31% (95% CI, 29%-34%).

- The GEC has a low positive predictive value (range, 13%-23%) in the context of a suspicious GEC result when NIFTP is factored in.

Molecular Testing

- MicroRNA analysis is a more recent method for molecular testing for which there are limited data but may prove to be useful in diagnostic decision making.

- Future refinement in molecular testing strategies is expected, with improved diagnostic performance

Molecular Testing

- Molecular testing is expensive, costing from between $3000 and $5000 per test in 2015, depending on the specific testing strategy.

- Several studies suggested that molecular testing using the GEC is cost-effective, primarily because of a decrease in the number of diagnostic surgeries and their associated complications when the test results are negative.

Molecular Testing

- However, most of these analyses are based on simulation modeling rather than on actual patient data, and the results vary depending on the test performance parameters, malignancy rates in the patient population, anticipated surgical procedure, surgical complication rates, health care setting, and other factors.

Four Possible Clinical Outcomes

Excellent Response

No clinical, biochemical, or structural evidence of disease

Biochemical Incomplete Response

Persistent abnormal thyroglobulin values in the absence of localizable disease

Structural Incomplete Response

Persistent or newly identified loco-regional or distant metastases

Indeterminate Response (Acceptable)

Non-specific biochemical or structural findings which cannot be confidently classified as either benign or malignant