European Thyroid JOURNAL

C Durante, L Hegedüs *et al.* | 12:5 | e230067

GUIDELINES

2023 European Thyroid Association Clinical Practice Guidelines for thyroid nodule management

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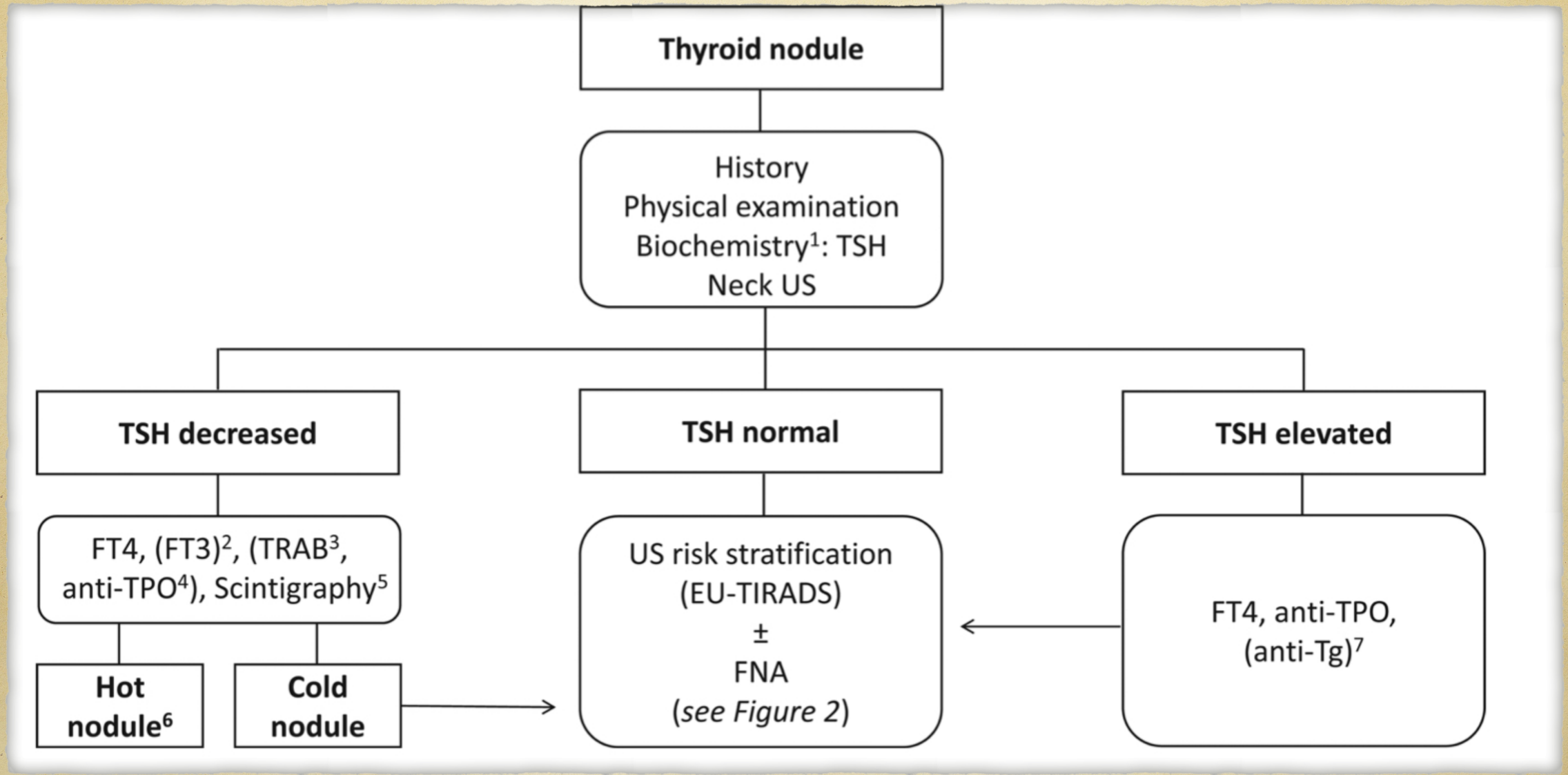
Initial evaluation

- combination of personal and family history, physical examination, evaluation of thyroid function, and US of the neck
- As a minimum, laboratory assessment TSH measurement.
- If TSH is **decreased**, we recommend determining **FT4**. If the latter is normal, **free T3** should be measured. Based on the clinical context, TSH receptor antibody determination may be considered to define the etiology of hyperthyroidism.
- If TSH is **elevated**, **FT4** and antithyroid peroxidase (**TPO**) antibodies should be measured to aid in the classification of the etiology of thyroid dysfunction.
- In case of clinical or US suspicion of chronic lymphocytic thyroiditis and **negative** anti-**TPO** antibodies, measurement of anti-thyroglobulin (**Tg) antibodies** may be considered


Thyroid nodule
History
Physical examination
Biochemistry[1]: TSH
Neck US
TSH decreased
TSH normal
TSH elevated
FT4, (FT3)[2], (TRAB[3], anti-TPO[4]), Scintigraphy[5]
Hot nodule[6]
Cold nodule
US risk stratification (EU-TIRADS) ± FNA (see Figure 2)
FT4, anti-TPO, (anti-Tg)[7]

- Using **calcitonin** for MTC screening in unselected thyroid nodule populations provides an early diagnosis and thereby potentially improves prognosis but screening is still under debate,
- In the **following scenarios, calcitonin** evaluation is appropriate:
- patients with thyroid nodules scheduled for surgery or MIT
- thyroid nodules with **indeterminate cytology or suspicious US findings**
- personal or family history of medullary thyroid cancer or multiple endocrine neoplasia type 2 .
- Cut-off points to separate non-medullary reasons for increased calcitonin from MTC have been established (**>30 pg/mL in females and >34 pg/mL in males**, even if several variables may affect this threshold)

- Serum Tg and Tg antibody determination has no role in the initial evaluation of nodular thyroid disease

Thyroid ultrasound

- Diagnostic thyroid and neck US should be performed in all patients clinically suspected of having nodular thyroid disease, or if a nodule is incidentally detected using another imaging modality (e.g. US scan of carotid arteries, CT of the neck)
- Anatomical regions to be evaluated:
- The thyroid bed and anterior neck from hyoid bone to sternal notch and below, if accessible.
- From levels II to V in the lateral neck and level VI in the central neck for lymph nodes
- A high-frequency linear probe (e.g. up to 14 MHz) is adequate for exploring these regions. To visualize the inferior pole of an intrathoracic thyroid a convex probe (frequency range: 2.5–5.0 MHz) may be useful

Table 2 Elements of thyroid ultrasound reporting in nodular thyroid disease.

Thyroid lobes	Echogenicity
	Size (three diameters and volume)
	Presence of substernal extension or compression of cervical structures
Nodule	Size (three diameters and volume)
	Location (according to the three axes)
	Echogenicity
	Composition
	Suspicious and non-suspicious signs if present[a]
	Possible extrathyroidal extension
Which discrete lesions should be described?	Nodules larger than 10 mm.
	Nodules between 5 and 10 mm with suspicious signs
How many nodules should be described in detail?	The largest one and those with suspicious signs if the number of nodules is >3 in a lobe[b]
Pathological[c] lymph nodes if present	Location, three diameters, features

[a]Suspicious ultrasound characteristics: microcalcifications, irregular margins, nonparallel orientation, marked hypoechogenicity of the solid part. Non-suspicious ultrasound characteristic: thin halo, macrocalcification (specify rim calcification)

[b]The propensity to offer surgery increases with number of suspicious nodules.

[c]Features of high suspicion are the presence of cystic areas, microcalcifications, thyroid tissue-like appearance, and anarchic vascularity in the absence of a visible hilum (15).

Thyroid ultrasound
Follow-up of untreated thyroid nodule(s)

- (a) Monitor growth (an increase ≥20% in at least two nodule diameters with a minimum increase of 2 mm, or nodule volume increase >50% at the time of re-evaluation) of thyroid nodule(s)
- (b) Monitor US feature changes that may modify risk stratification.
- (c) Monitor lateral neck lymph nodes.
- (d) Re-evaluate in case of the appearance of local pressure symptoms and/or voice changes.

Complementary ultrasound techniques Doppler imaging

- The usefulness of the Doppler vascular pattern for defining the risk of malignancy (ROM) of thyroid nodules is **controversial**
- Doppler imaging may be indicated in order to differentiate **between** cases where **vascularization is diminished or absent (e.g. thick colloid, cystic or necrotic nodules) from solid nodules**
- **So**, it may indirectly be useful for risk stratification and for guiding FNA and minimally invasive procedures in mixed thyroid lesions.

Elasto-sonography

- The role of elastography remains unsettled.
- **classical** variant of papillary thyroid carcinoma (PTC) has demonstrated **high stiffness,** other variants of PTC and FTC may show a **normal** stiffness
- Thus, the contribution of this method to the standard US imaging does not justify its routine use and inclusion in the risk stratification systems (RSSs).

Contrast-enhanced ultrasound

- A few meta-analyses report that CEUS has a rather high positive and negative predictive value for the assessment of the ROM
- their use is limited because contrast agents are expensive, invasive, and not universally licensed for this purpose.
- However, CEUS provides a clear depiction of the **ablated areas after thermal ablation (TA)** of thyroid nodules and offers an advantage for guiding the need for repeat treatments

Thyroid Imaging and Reporting Data System(TIRADS)

- all TIRADS **reduce the number of unnecessary FNAs**, the preferred system is the EU-TIRADS
- users should be aware of the following:
- (a) TIRADS have been designed and mainly tested for **PTCs**, although they are proposed to estimate the malignancy risk of any thyroid neoplasm. The sensitivity for the detection of the **classical variant is excellent** but **decreases** substantially for the **follicular variant and even more for FTCs .** Accuracy in identifying **medullary** thyroid carcinomas is debated
- (b) **Misdiagnoses** may occur, especially in **cystic nodules** and **in sub-acute as well as chronic thyroiditis**
- (c) **Composition** of the nodule is **not included** in the **cardinal** features of the **EU**-TIRADS. However, the users should consider that the ROM is higher in completely solid than mainly cystic ones

- (d) Ultrasound features suggestive of **extra-thyroidal extension (i.e. capsular bulging, disruption, or abutment by the thyroid nodule**) are **not included** in the cardinal features of the EU-TIRADS. However, they should be described in the report as they are associated with a higher ROM and **should prompt FNA irrespectively of EU-TIRADS score**

- (e) When using EU-TIRADS and in case of difficulties with ascertaining the presence of features of high suspicion, we suggest classifying **these nodules as EU-TIRADS 4**

- (f) TIRADS scores do **not include lymph node** evaluation. Cervical lymph nodes should be described as normal, indeterminate, or suspicious, and located using the six cervical levels nomenclature (Fig. 3). Features of **high suspicion** are the presence of **cystic areas, microcalcifications, thyroid tissue-like appearance, and anarchic vascularity in the absence of a visible hilum**

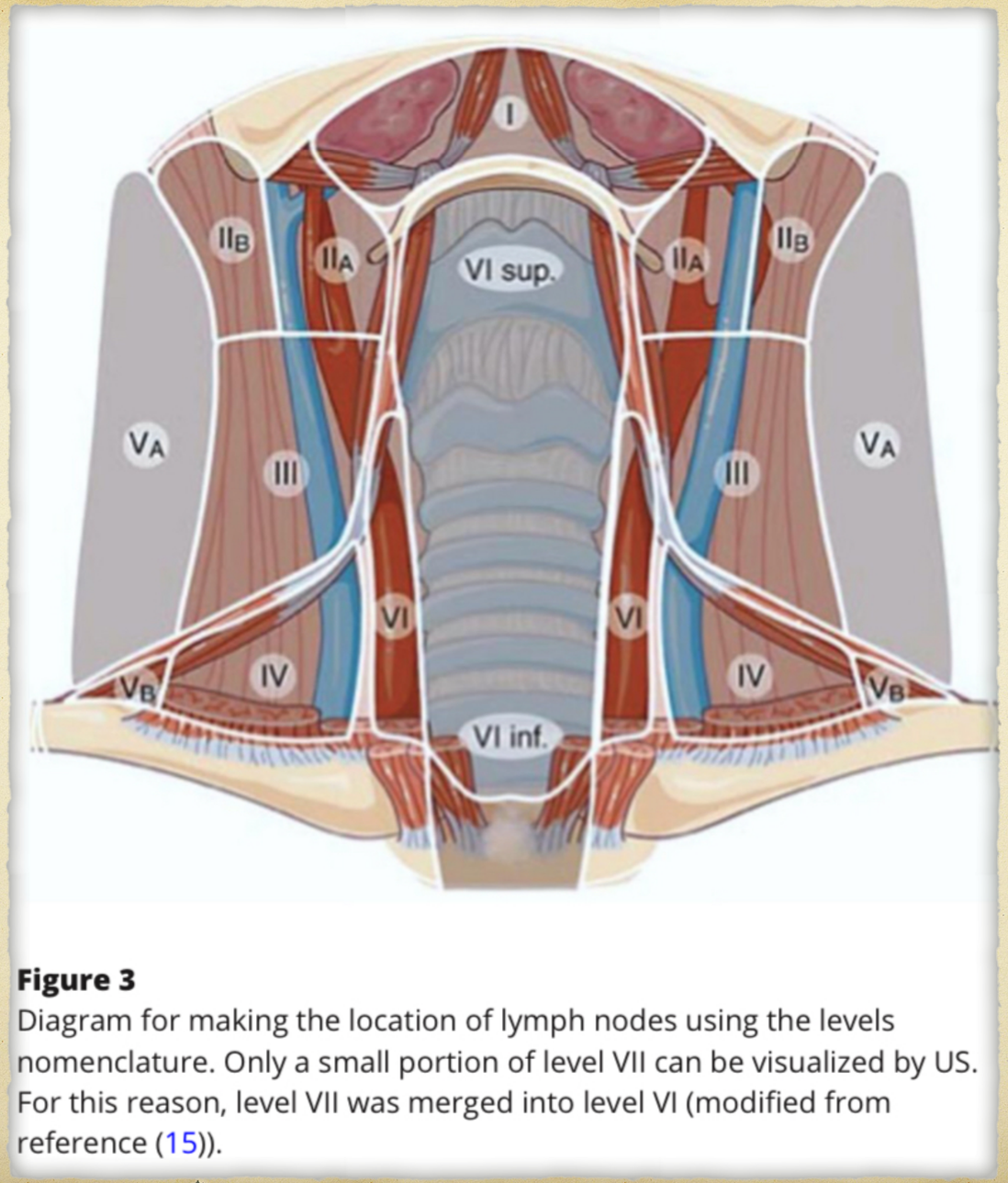


Figure 3
Diagram for making the location of lymph nodes using the levels nomenclature. Only a small portion of level VII can be visualized by US. For this reason, level VII was merged into level VI (modified from reference (15)).

Fine-needle aspiration

- The indications for FNA, **based on EU-TIRADS**, and the **factors that may influence this choice** are described in Tables **3 and 4**, respectively
- **Severe coagulation disorders** represent a contraindication to FNA, while the use of anticoagulant therapy does not, as long as **INR is below 3**.
- Antiaggregant therapy is not an absolute contraindication to FNA.
- Unless highly suspicious for malignancy, hyperfunctioning thyroid nodules should not be biopsied
- **Scintigraphy should be performe**d in case of **subnormal serum TSH,** with or without elevated free thyroid hormones
- In certain situations, **scintigraphy may be warranted also when TSH is normal (**e.g. in current or formerly iodine deficient regions and in case of a multinodular goiter). The reasons mainly being to decide eligibility for FNA and/or radioactive iodine (RAI) treatment.

Table 3 EU-TIRADS categories with corresponding malignancy risks and indication of fine-needle aspiration cytology.

Category	Ultrasound features[a]	Estimated malignancy risk according to ETA guidelines (%)	Observed malignancy risk vs surgery (127)	FNA[b]
EU-TIRADS 1: normal	No nodule	None		No
EU-TIRADS 2: benign	Pure cyst Entirely spongiform	0	1.4	No, unless scheduled for treatment
EU-TIRADS 3: low risk	Iso/hyperechoic No feature of high suspicion	2–4	3.5	If >20 mm
EU-TIRADS 4: intermediate risk	Mildly hypoechoic No feature of high suspicion	6–17	17	If >15 mm
EU-TIRADS 5: high risk	At least one of the following features of high suspicion: • Irregular shape • Irregular margins • Microcalcifications • Marked hypoechogenicity	26–87	87.7	If >10 mm[c]

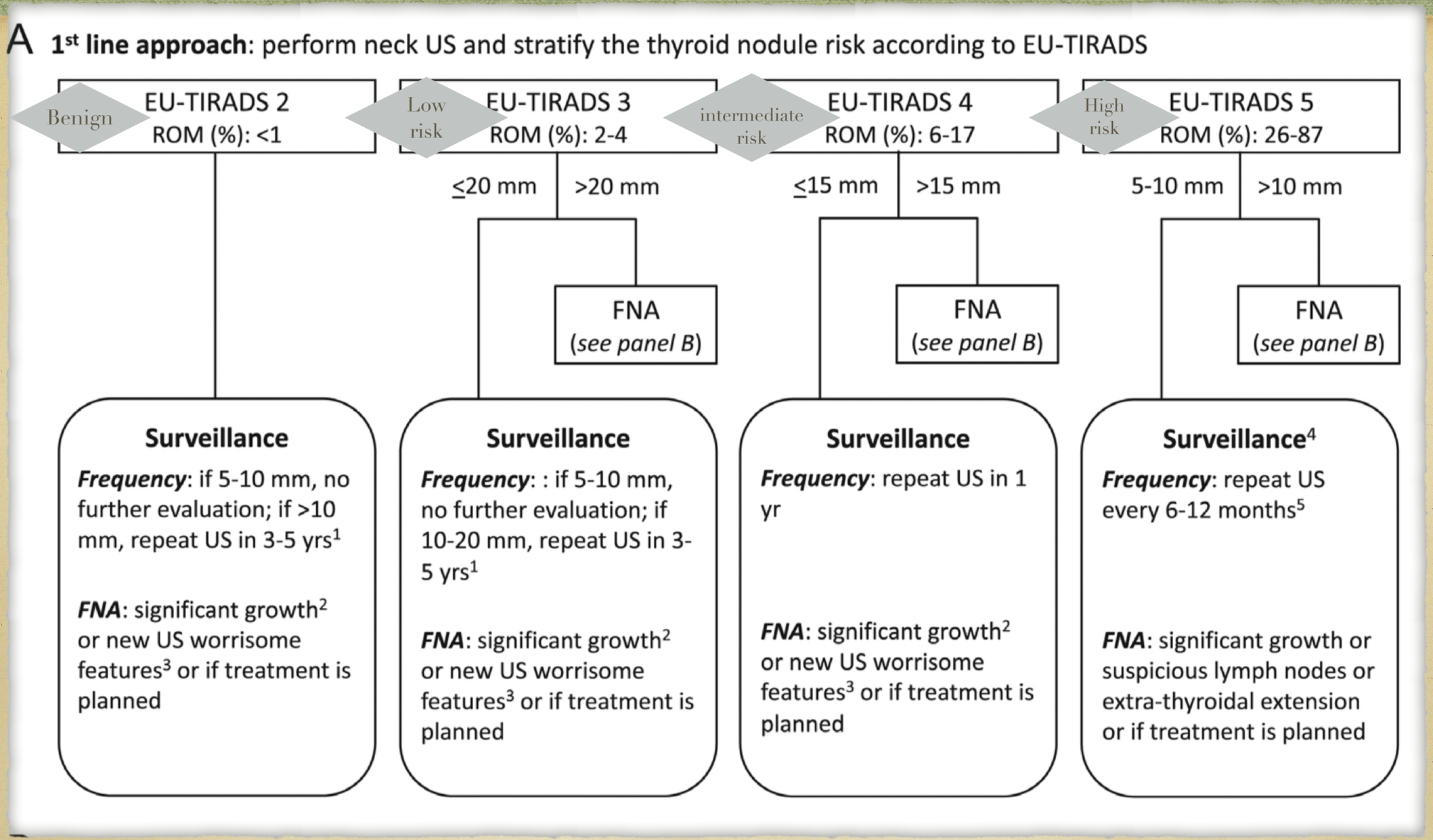
[a]If difficulties with ascertaining the presence of features of high suspicion, we suggest classifying these nodules as EU-TIRADS 4.

[b]FNA should be performed in nodules irrespectively of EU-TIRADS score if either pathological lymph nodes are present or the nodule is suspicious of extra-thyroidal extension.

[c]For 5–10 mm high suspicion nodules, FNA should be considered if there are suspicious lymph nodes or if there is suspicion of extra-thyroidal extension.

Table 4 Criteria other than size and US risk level, which strengthen or weaken the indication for fine-needle aspiration.

	Strengthens FNA	Weakens FNA
Clinical factors	• Male sex • Young age • Solitary nodule • Compressive symptoms related to the nodule • Family history of medullary thyroid cancer or MEN2 • Head and neck radiation during childhood • Planned thyroid or parathyroid surgery • Patient preference	• Long personal history of stable or slowly growing MNG • Limited life expectancy • Significant comorbidity • Patient preference • Family history of benign nodular thyroid disease
Genetic factors	• Monogenic syndromic thyroid susceptibility • Strong family history of thyroid cancer (>2 relatives)	
Biological tests	• Elevated serum calcitonin • Calcitonin responsive to stimulation test in RET gene carriers	• Subnormal thyrotropin
Nuclear medicine imaging	• 18-FDG uptake • MIBI uptake	• Autonomous nodules on isotope scan



For 5–10 mm EU-TIRADS 5 nodules, FNA is recommended if there are suspicious lymph nodes, risk of extra-thyroidal extension, or location in worrisome areas (e.g. close to trachea, laryngeal nerve area).

Fine-needle aspiration

- FNA should be **repeated** in case of:
- a first non-diagnostic sample
- a Bethesda class III cytology
- discrepancy between US risk score (i.e. high risk) and cytological findings (i.e. benign cytology)
- significant nodule growth

Core-needle biopsy

- There are no clear advantages of using CNB, a more invasive and expensive procedure compared to FNA, based on cost and risk–benefit analysis
- CNB may be considered in the following situations:
- **repeat inadequate FNA as an alternative to diagnostic surgery**
- **repeat Bethesda class III cytology**
- when histological assessment can improve preoperative diagnosis (e.g. **suspicion of poorly differentiated or undifferentiated thyroid cancer, thyroid lymphoma, thyroid metastases)**

Wash-out thyroglobulin, calcitonin, and parathyroid hormone determination

- In patients suspected of **lymph node metastases,** diagnostic **confirmation** should be obtained by **US-guided FNA**, before offering therapy
- In the case of DTC, Tg washout determination should be added,in the case of MTC, calcitonin measurement
- In some cases of small **nodules** with normal serum calcitonin but cytological suspicion of MTC or in case of elevated serum calcitonin, **calcitonin washout** assessment of the **nodule** can be useful
- In the rare cases of **intranodular parathyroid adenomas,** parathyroid hormone determination in FNA washout may confirm the clinical suspicion

Pathology
Cytopathology

- most widely used system is ‘The 2017 Bethesda System for Reporting Thyroid Cytopathology’ (TBSRTC),
- Minimum requirements for a thyroid FNA cytopathology report:
- Identification of the patient
- Imaging findings and, if available, TIRADS score
- Adequacy of the sample
- Microscopic description of the material including cellular and colloid components
- Ancillary testing (if performed)
- Reporting category and subclassification (specific diagnosis)
- local ROM of the diagnostic category

Bethesda categories	Definition of Bethesda categories	Subclassification		Expected frequency (range)	Estimated malignancy risk (NIFTP not cancer)
		Benign entities	Malignant entities		
Bethesda I	Non-diagnostic	NA	NA	3–11%	5–10%
Bethesda II	Benign	Adenomatoid/hyperplastic/colloid nodule Lymphocytic thyroiditis Subacute granulomatous thyroiditis Acute thyroiditis Graves' disease	PTC microcarcinomas in benign nodules	55–74%	0–3%
Bethesda III	Atypia of undetermined significance or follicular lesion of undetermined significance (AUS/FLUS)	Cyst lining cells Hashimoto's thyroiditis with cellular atypia (both follicular and lymphocytic atypia) Adenomatoid nodule (cellular with microfollicular proliferation) Parathyroid adenoma (microfollicular structures) Hürthle cell hyperplasia with lack of colloid	PTC, especially follicular variant; well-differentiated follicular carcinoma; Hürthle cell carcinoma; lymphoma	5–15%	10–30%
Bethesda IV	Follicular neoplasm or suspicious for follicular neoplasm (FN/SFN)	Adenomatoid nodule (cellular with microfollicular proliferation) Parathyroid adenoma (microfollicular structures) Hürthle cell hyperplasia with lack of colloid Follicular-patterned cases with mild nuclear changes (increased nuclear size, nuclear contour irregularity, and/or chromatin clearing), and lacking true papillae and intranuclear pseudo-inclusions	PTC, especially follicular variant; well-differentiated follicular carcinoma; Hürthle cell carcinoma	2–25%	25–40%
Bethesda V	Suspicious of malignancy	Hashimoto's thyroiditis with cellular atypia	Features suspicious for PTC, MTC, lymphoma, or other malignancy	1–6%	50–75%
Bethesda VI	Malignant	Hashimoto's thyroiditis with cellular atypia	Features *conclusive* for malignancy: PTC (true papillae, psammoma bodies, nuclear pseudo-inclusions) MTC, poorly differentiated/ATC, non-endocrine malignancy (squamous cell, lymphoma,	2–5%	97–99%

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Non diagnostic	Benign	AUS/ FLUS	FN/SFN	Suspicious of malignancy	Malignant
BETHESDA I ROM (%): 1-4	BETHESDA II ROM (%): <3	BETHESDA III ROM (%): 5-15	BETHESDA IV ROM (%): 15-30	BETHESDA V ROM (%): 60-75	BETHESDA VI ROM (%): 97-99
EU-TIRADS 3 (*>20 mm*) ***Repeat FNA:***[1] *if still Bethesda class I, consider* ***CNB****.* **EU-TIRADS 4 (*>15 mm*) and 5 (*>10 mm*)** ***Repeat FNA:***[1] *if still Bethesda class I, consider* ***CNB*** *or molecular testing (if available and sufficient material).*	**EU-TIRADS 3 (*>20 mm*) and 4 (*>15 mm*)** **Repeat US** in 3-5 yrs[2] ***Repeat FNA***[1,3] *if* significant growth[4] or new worrisome features **EU-TIRADS 5 (*>10 mm*)** ***Repeat FNA***[1,5] *(imaging and pathology not concordant)*	**EU-TIRADS 3 (*>10 mm*)** ***Repeat FNA:***[1] *if still Bethesda class III, repeat US within 1 yr or consider molecular testing (if available) or offer surgery* **EU-TIRADS 4 and 5 (*>10 mm*)** ***Repeat FNA:***[1] *if still Bethesda class III, offer surgery, or surveillance, or molecular testing (if available)*	**EU-TIRADS 3, 4 and 5 (*>10 mm*)** *Offer surgery or molecular testing (if available)*[6] In the case of 5–10 mm EU-TIRADS 5 and Bethesda class IV, <u>surveillance</u> may be offered as an alternative option.	**EU-TIRADS 3, 4 and 5 (*>10 mm*)** *Recommend:* ▪ *Surgery*[7] In the case of 5–10 mm EU-TIRADS 3, 4, and 5 and Bethesda class V or VI, surveillance or <u>minimally invasive treatment</u> may be offered as alternative options in the absence of suspected lymph node involvement or extra-thyroidal extension.	

Molecular diagnostics applied to cytology

- Molecular testing may be considered in cytologically **indeterminate** nodules, if available (Strength of recommendation: 1)

- Three of the widely available molecular testing approaches include mutational analysis (ThyroSeq v3), mRNA genomic expression (Afirma genomic sequencing classifier [GSC]), and a combination of microRNA (miRNA) gene expression and mutational analysis (ThyraMIR/ThyGenX)

- Up to 13.4% **avoided diagnostic surgeries** have been reported for the ThyroSeq and the Afirma GSC

Table 6 Summary of genetic tests for aiding diagnosis of thyroid cancer in FNA cytology.

	Afirma GSC	ThyroSeq v3	ThyGeNEXT/ThyraMIR	ThyroidPrint
Type of test	RNA NGS (mRNA expression)	Targeted DNA and RNA NGS	Targeted NGS + miRNA expression	Quantitative real-time PCR (mRNA expression)
Biomarkers	1115 genes (expression) + mutation hotspots + fusions + LOH	112 genes + >120 fusions + 10 CNA + 19 genes (expression)	10 genes + 28 fusions + 10 miRNA (expression)	10 genes
NPV in marketing study (%)	96%	97%	95%	95%
PPV in marketing study (%)	47%	66%	74%	78%
Sensitivity in marketing study (%)	91%	94%	93%	91%
Specificity in marketing study (%)	68%	82%	90%	88%
Sample size Bethesda III, IV (n)	114, 76	154, 93	92, 86	117, 153
Advantages	Some independent validation studies	Most comprehensive mutation and CNA coverage, highest NPV in marketing study of commercially available tests	Best ROM stratification for *RAS*-positive nodules	Marketing study included a trial in South America and a trial in North America, highest PPV in marketing study of commercially available tests
Disadvantages	Mutation coverage is less sensitive because it uses RNA rather than DNA sequencing	A single-center study has shown a doubling in indeterminate thyroid nodule diagnosis following the implementation of ThyroSeq (128)	A 'moderate' test result in 21% of samples provides no clarity on diagnosis since the moderate category has a 39% risk of malignancy	No mutation data, no independent validation to date
Validation study	Patel *et al.* (2018) (84)	Steward *et al.* (2019) (85)	Lupo *et al.* (2020) (86)	Zafereo *et al.* (2020) (129)
Validation concerns	Post-marketing studies have conflicting results on NPV as resected nodules in the validation cohort are not representative of all indeterminate thyroid nodules (130). This results in unclear real-world benefit. In case of availability of similar post-marketing studies for the	Few post-marketing studies result in unclear real-world benefit, since they have been concentrated at tertiary centers not representative of all practices.	No independent validation means there is no evidence of reproducibility of the diagnostic performance reported. Retrospective design of the validation study.	No independent validation means there is no evidence of reproducibility of the diagnostic performance reported. The 'kit' design rather than centralizing testing introduces the

- **high risk** molecular profiles (e.g. coexistence of either BRAF p.V600E or RAS mutations with late-hit mutations like those in TERT promoter, PIK3CA or TP53 genes) have been strongly associated with the presence of distant metastases in DTC patients thus increasing the odds of an indeterminate thyroid nodule with high-risk mutations being aggressive cancer.

Thyroid scintigraphy

- For routine use, most often 99mTc is used, based on a combination of low cost, wide availability, and low radiation burden.
- in a minority, this approach may lead to the **misclassification of hypofunctioning as hyperfunctioning nodules**
- Thyroid scintigraphy should be performed when serum TSH is suppressed or at the lower normal limits.
- Of note, **in areas of current or previous iodine deficiency, hyperfunctioning nodules may also be seen in individuals with normal TSH, meriting the use of thyroid scintigraphy**

Thyroid scintigraphy

- While we do not suggest [**99mTc]Tc-MIB**I imaging for routine use, it may be of value in case of indeterminate cytology, based on its relatively high negative predictive value for malignancy
- Similarly, in patients with indeterminate cytology,[**18 F]FDG-PET/CT**, although still debated, has shown promising results for excluding malignancy

Thyroid scintigraphy

- Thyroid scintigraphy provides useful information in:
- solitary hyperfunctioning nodules, to avoid FNA, as hyperfunctioning nodules are rarely malignant;
- multinodular goiter, to differentiate hypofunctioning nodules suitable for FNA from hyperfunctioning lesions that do not need cytologic evaluation;
- to determine the eligibility for radioiodine therapy.

Other imaging modalities

- **incidentally** detected thyroid lesions do have a ROM of **5–13%** when using CT and MRI and of about **35%** of high activity lesions when using [18 F]FDG-PET/CT
- These types of nodules should be investigated according to the diagnostic workup proposed in this guideline.
- Neck and upper mediastinal CT scan should be performed in case of US or clinical suspicion of substernal extension.
- If using contrast media, the risk of thyrotoxicosis should be considered.

Therapeutic options: non-surgical approaches

- In the absence of elevated TSH, the use of thyroid hormone in order to decrease TSH should be discouraged in order to limit the increased morbidity and mortality seen with such therapy
- Iodine as well as selenium deficiency is associated with increased goiter prevalence. However, neither iodine nor selenium supplementation is recommended in iodine and selenium replete populations.

Radioiodine therapy

- 5–10% of solitary/dominant thyroid nodules are functioning on thyroid scintigraphy
- Such nodules are, with extremely rare exceptions, **benign**, should **not be biopsied**, and are **eligible for RAI** treatment.
- Most patients are **euthyroid or subclinically hyperthyroid** at the time of diagnosis.
- severely hyperthyroid or with cardiac comorbidity, need pre-treatment with anti-thyroid drugs.
- RAI is most often given as a fixed activity (e.g. 185–370 MBq), most often achieves euthyroidism, may cause hypothyroidism, and **reduces nodule size by 30–50% in 12 months**
- **Life-long follow-up is recommended.**

- The diagnostic workup of **non-hyperfunctioning multinodular goiters**, including FNA, should accord with the previously described algorithm (Figs. 1 and 2).
- When **symptomatic** and **benign**, thyroid nodules may, as an alternative to surgery, be eligible for RAI, especially in case of patients at surgical risk.
- Hypothyroidism is rare (10–20% after 10 years), but lifelong follow-up is recommended.
- Thyroid volume is typically reduced by 40% within 12 months and alleviates symptoms in most.
- In case of low RAI uptake and/or a large goiter, prestimulation with rhTSH has been demonstrated to augment thyroid volume reduction by 35% and improves pulmonary function, and reduces pressure symptoms

Minimally invasive techniques

- for non-surgical management of thyroid lesions that cause **local pressure symptoms** or **esthetic** concerns
- MITs include **ethanol ablation (EA)**, based on the direct injection of ethanol into a **cystic** cavity, and **TA techniques**, which use various energy sources: laser, radiofrequency, microwaves, or highintensity focused ultrasound
- MITs result in a relevant and long-lasting decrease of nodule volume (57-77% at 5 years) that is paralleled by improvement of local symptoms and disease-related quality of life

- **EA** is preferred as an effective, safe, and inexpensive treatment for **cystic (or predominantly cystic) symptomatic** thyroid nodules
- while **TA** procedures, due to their geometric and predictable volume of tissue destruction, are the first-line treatment for **solid thyroid lesions**

- Consider **TA** for the treatment of **solid benign** thyroid nodules that cause local **symptoms** as an alternative to surgery and for cystic lesions that relapse after EA
- **TA** is an alternative to RAI and surgery in **small hyperfunctioning nodules (<10 mL),** while it performs **poorer in larger nodules**
- Currently, a major limitation of TA procedures use is their limited availability and lack of long-term data
- After MIT, follow-up patients with clinical, biochemical and US assessments after 6 and 12 months. Re-evaluate the patient after 3–5 years

Therapeutic options: surgical approach

- surgery may be appropriate in the following scenarios:
- **Symptomatic** nodular thyroid disease, as an alternative option to MIT and RAI therapy.
- Nodules as **benign** at cytology and/or **low risk at US** (i.e. EU-TIRADS 2 or 3) and **become symptomatic over time (airway or esophagus compression),** in case of **cosmetic** concern, **retro-clavicular and mediastinal extension**.
- In **benign** lesions (Bethesda class **II cytology**), even if asymptomatic, **nodules ≥4 cm (due to the ROM and increased probability of a false negative FNA)**
- Nodules with **indeterminate cytology (Bethesda class III and IV)** that are not suitable for active surveillance (i.e. **large size, high suspicion of malignancy on US, symptomatology).**
- Nodules with a Bethesda **class V and VI cytology.**
- **Calcitonin levels higher than the established cut-off**

Therapeutic options: surgical approach

- For nodules of uncertain malignant potential (Bethesda class III–V cytology), surgery allows for a definitive diagnosis .
- Molecular test results (if available) should be considered prior to operation .
- For diseases limited to one lobe, lobectomy/hemithyroidectomy is recommended. If such a disease is diagnosed in a **nodular goiter**, near-total thyroidectomy should be considered.
-

- When **surgery** is considered for patients with a solitary, cytologically **indeterminate** nodule, thyroid **lobectomy** is the recommended initial surgical approach.

- **total thyroidectomy** may be preferred in patients with **indeterminate** nodules that are cytologically suspicious for malignancy, positive for known mutations specific for carcinoma, sonographically suspicious, or large (>4 cm), or in patients with familial thyroid carcinoma or history of radiation exposure, as well as patient preference, presence of contralateral nodularity or coexistent hyperthyroidism

THYROID
Volume 33, Number 9, 2023

DOI: 10.1089/thy.2023.0141

SPECIAL ARTICLE

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The 2023 Bethesda System for Reporting Thyroid Cytopathology

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- The most important is the assignment of a single name for each of the 6 diagnostic categories: (i) nondiagnostic; (ii) benign; (iii) atypia of undetermined significance; (iv) follicular neoplasm; (v) suspicious for malignancy; and (vi) malignant.
- The third edition offers an average ROM for each category, in addition to the expected range of cancer risk.
- The atypia of undetermined significance subcategorization is simplified into 2 subgroups based on the implied ROM and molecular profiling.
- A discussion of pediatric thyroid disease has been added

- TBSRTC 2023 recommending a single designation for each of the 6 categories, **discontinuing** the previously used terms of “unsatisfactory,” “follicular lesion of undetermined significance,” and “suspicious for a follicular neoplasm.”

- TBSRTC 2023 recommends the following as the 6 reporting category names: (i) nondiagnostic; (ii) benign; (iii) atypia of undetermined significance (AUS); (iv) follicular neoplasm; (v) suspicious for malignancy (SFM); and (vi) malignant (Table 1).
- TBSRTC 2023 continues to recommend that the names of the categories (and not just their numerical designations) should be used for reporting results and publishing scientific investigations to avoid confusion
- Adding a category number after the category name is an acceptable, optional practice (e.g., benign [Bethesda II], AUS [Bethesda III]).

- Based on new prospective studies since the publication of the second edition, the revised ROM for each category when excluding NIFTP is shown in Table 4, information that could help guide more conservative clinical management of some nodules.

Table 1. The 2023 Bethesda System for Reporting Thyroid Cytopathology: Diagnostic Categories

I. Nondiagnostic
- Cyst fluid only
- Virtually acellular specimen
- Other (obscuring blood, clotting artifact, drying artifact, etc.)

II. Benign
- Consistent with follicular nodular disease (includes adenomatoid nodule, colloid nodule, etc.)
- Consistent with chronic lymphocytic (Hashimoto) thyroiditis in the proper clinical context
- Consistent with granulomatous (subacute) thyroiditis
- Other

III. Atypia of undetermined significance
- Specify if AUS-nuclear atypia or AUS-other

IV. Follicular neoplasm
- Specify if oncocytic (formerly Hürthle cell) type

V. Suspicious for malignancy
- Suspicious for papillary thyroid carcinoma
- Suspicious for medullary thyroid carcinoma
- Suspicious for metastatic carcinoma
- Suspicious for lymphoma
- Other

VI. Malignant
- Papillary thyroid carcinoma
- High-grade follicular-derived carcinoma
- Medullary thyroid carcinoma
- Undifferentiated (anaplastic) carcinoma
- Squamous cell carcinoma
- Carcinoma with mixed features (specify)
- Metastatic malignancy
- Non-Hodgkin lymphoma
- Other

TABLE 2. THE 2023 BETHESDA SYSTEM FOR REPORTING THYROID CYTOPATHOLOGY: IMPLIED RISK OF MALIGNANCY WITH EXPECTED RANGES BASED ON FOLLOW-UP OF SURGICALLY RESECTED NODULES WITH RECOMMENDED CLINICAL MANAGEMENT

Diagnostic category	*ROM*[a] *Mean % (range)*	*Usual management*[b]
Nondiagnostic	**13** (5–20)[c]	Repeat FNA[d] with ultrasound guidance
Benign	**4** (2–7)[e]	Clinical and ultrasound follow-up
Atypia of undetermined significance[f]	**22** (13–30)	Repeat FNA,[d] molecular testing, diagnostic lobectomy, or surveillance
Follicular neoplasm[g]	**30** (23–34)	Molecular testing,[h] diagnostic lobectomy
Suspicious for malignancy	**74** (67–83)	Molecular testing,[h] lobectomy or near-total thyroidectomy[i]
Malignant	**97** (97–100)	Lobectomy or near-total thyroidectomy[i]

Adapted, with permission, from Ali and VanderLaan.[7]

[a]These ROM estimates are skewed by selection bias, because many thyroid nodules (especially those diagnosed as benign or atypia of undetermined significance) might not undergo surgical excision.

[b]Actual management could depend on other factors (e.g., clinical, ultrasound findings), in addition to the FNA interpretation.

[c]The ROM varies with the type and structure of the nodule (i.e., solid vs. complex vs. >50% cystic); nondiagnostic aspirates from solid nodules are associated with a higher ROM compared with those showing >50% cystic changes and low-risk ultrasound features.

[d]Studies have shown diagnostic resolution with repeat FNA.

[e]This ROM estimate is based on follow-up of surgically resected nodules, which is skewed by selection bias because most thyroid nodules classified as benign do not undergo surgical excision; using long-term follow-up studies, the best overall ROM estimate for a benign FNA is ~1% to 2%.

[f]This category can be further subclassified into specimens with nuclear versus non-nuclear atypia, the ROM appears to be higher for cases with nuclear atypia.

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

[h]Molecular analysis can be performed to assess the type of surgical procedure (lobectomy vs. total thyroidectomy).

Table 3. The 2023 Bethesda System for Reporting Thyroid Cytopathology in Pediatric Patients with Implied Risk of Malignancy and Possible Management Recommendations

Diagnostic category	*ROM mean % (range)*	*Possible management recommendations*
Nondiagnostic	14 (0–33)	Repeat FNA with ultrasound guidance
Benign[a]	6 (0–27)	Clinical and ultrasound follow-up
Atypia of undetermined significance	28 (11–54)	Repeat FNA or surgical resection
Follicular neoplasm[b]	50 (28–100)	Surgical resection
Suspicious for malignancy	81 (40–100)	Surgical resection
Malignant	98 (86–100)	Surgical resection

Table 4. Reported Decreases in the Risk of Malignancy of The Bethesda System for Reporting Thyroid Cytopathology Diagnostic Categories If Excluding Nodules Diagnosed by Surgical Pathologic Examination as Noninvasive Follicular Thyroid Neoplasm with Papillary Like Nuclear Features

Diagnostic category	*Decrease in ROM if excluding NIFTP*[a] *Mean % (range)*	*Estimated final ROM if excluding NIFTP*[b] *Mean %*
Nondiagnostic	1.3 (0–2)	12
Benign	2.4 (0–4)	2
Atypia of undetermined significance	6.4 (6–20)	16
Follicular neoplasm	7.1 (0.2–30)	23
Suspicious for malignancy	9.1 (0–40)	65
Malignant	2.6 (0–13)	94

Nondiagnostic

- discontinued of using the term "unsatisfactory" for the first category
- to recommend a minimum of **6** groups of well-preserved, with each group comprising ‡**10** cells, for an adequate sample (quantity).
- Aspirates that consist of **cyst fluid only** with or without macrophages continue to be interpreted as **nondiagnostic** (**Bethesda I).**
- A **repeat aspiratio**n is recommended for cytologically **nondiagnostic** nodules and will yield diagnostic results in **60%–80%** of cases
- lower diagnostic yields if the repeat FNA is performed sooner than **3 months.**
- **American Thyroid Association guidelines now state that there is no need to wait several months before repeating the FNA.**

Benign

- use of the term “**follicular nodular disease**” is preferred to refer to the spectrum of changes previously designated as colloid nodule, hyperplastic nodule, adenomatous nodule, or benign follicular nodule.

AUS

- AUS is one of the three “indeterminate” cytopathologic interpretations that convey a diagnosis that is not definitively benign or malignant
- AUS subcategorization into 2 groups: “**nuclear**” (previously “cytologic”) and “**other**.” The latter includes cases with **architectural atypia, oncocytic atypia, and lymphocytic atypia,**
- AUS with **nuclear atypia** has a significantly **higher** ROM compared with AUS associated with other patterns, particularly those characterized by **architectural atypia** alone or a predominance of **oncocytes**.

AUS

Nuclear atypia is commonly seen in hyperplastic nodular goiter, papillary cancer, follicular variant papillary cancer, and NIFTP

Architectural atypia is commonly seen in nodular goiter (including autonomous nodules), follicular neoplasms, follicular cancer, follicular variant papillary cancer, and NIFTP.

Oncocytic atypia is seen in degenerating nodular Hashimoto's thyroiditis, oncocytic neoplasms, and oncocytic cancer.

Follicular Neoplasm

- Follicular neoplasms may be benign follicular adenomas (including autonomous nodules), follicular cancers, follicular variant papillary cancers, follicular neoplasms with oncocytic features (formerly Hürthle cell neoplasm), or NIFTP.
- approximately **30%** of cases diagnosed as follicular neoplasm (Bethesda IV) on FNA **turn out to be benign follicular nodular disease** on surgical resection
- recommended **management** of follicular neoplasm is surgical excision of the nodule, most often hemithyroidectomy or lobectomy.

Suspicious for Malignancy

- SFM (Bethesda V) is used when the cytomorphologic features of a thyroid FNA are worrisome for papillary thyroid carcinoma, medullary thy- roid carcinoma, lymphoma, or another malignant neoplasm but are quantitatively and/or qualitatively *insufficient* for a definitive malignant (Bethesda VI) diagnosis.
- **Some**, but not all, of the cases in this category raise the **possibility of a follicular variant of papillary thyroid carcinoma or NIFTP.**
- In such cases, deescalating the surgical management with lobectomy rather than total thyroidectomy could be a good approach.

Malignant

- term “papillary thyroid carcinoma, variants” is now changed to “papillary thyroid carcinoma, subtypes”
- new term “high-grade follicular-derived thyroid carcinoma” is now endorsed, which replaces the older nomenclature of “poorly differentiated thyroid carcinoma.”

با تشکر از توجه شما