IN THE NAME OF GOD

Journal club presentation

2023 European Thyroid Association Clinical Practice Guidelines for thyroid nodule management

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Title: 2023 European Thyroid Association Clinical Practice Guidelines for Thyroid Nodule Management

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Introduction

- Thyroid nodules are common, with up to 60% of adults having one or more
- Most nodules are benign and asymptomatic
- Malignancy risk is 1-5% in unselected populations
- Need for cost-effective, risk-adapted management approaches
- Importance of patient preference in decision-making

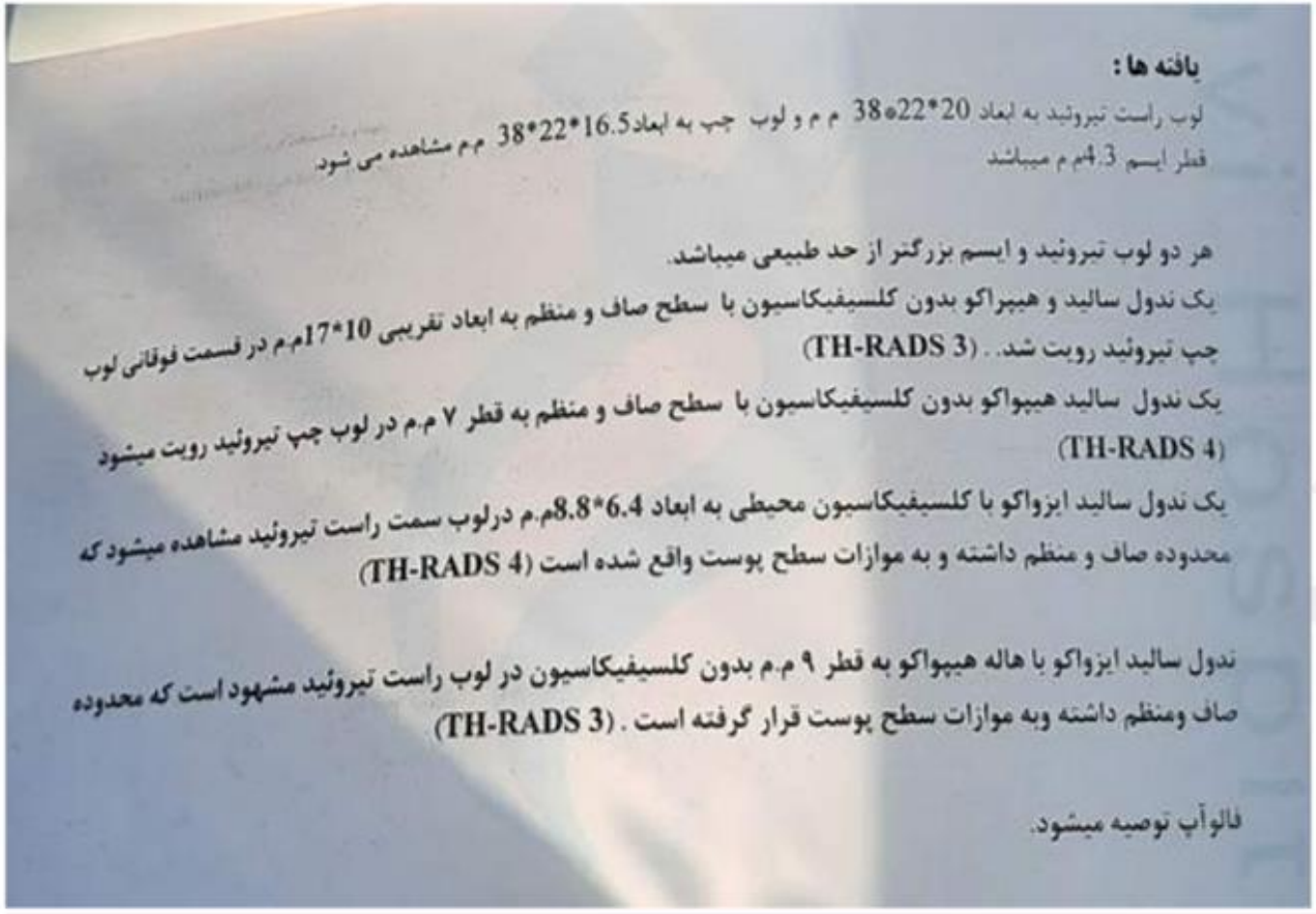
Methodology

- Multidisciplinary team of experts commissioned by ETA
- Systematic literature search using MEDLINE/PubMed
- GRADE framework used for grading evidence and recommendations
- Modified Delphi process for consensus on recommendations
- Incorporation of previous ETA guidelines where appropriate

Case

A 46-year-old female without a thyroid history who presents with an ultrasound report for her routine checkup tests. During her visit, she reports no symptoms in her daily life.

TSH: 1 T4: 7 T3: 90



یافته ها :

لوب راست تیروئید به ابعاد 38*22*20 م م و لوب چپ به ابعاد38*22*16.5 م.م مشاهده می شود.
قطر ایسم 4.3م م میباشد

هر دو لوب تیروئید و ایسم بزرگتر از حد طبیعی میباشد.

یک ندول سالید و هیپراکو بدون کلسیفیکاسیون با سطح صاف و منظم به ابعاد تقریبی 10*17م.م در قسمت فوقانی لوب چپ تیروئید رویت شد. . (TH-RADS 3)

یک ندول سالید هیپواکو بدون کلسیفیکاسیون با سطح صاف و منظم به قطر ۷ م.م در لوب چپ تیروئید رویت میشود (TH-RADS 4)

یک ندول سالید ایزواکو با کلسیفیکاسیون محیطی به ابعاد 6.4*8.8م.م درلوب سمت راست تیروئید مشاهده میشود که محدوده صاف و منظم داشته و به موازات سطح پوست واقع شده است (TH-RADS 4)

ندول سالید ایزواکو با هاله هیپواکو به قطر ۹ م.م بدون کلسیفیکاسیون در لوب راست تیروئید مشهود است که محدوده صاف ومنظم داشته وبه موازات سطح پوست قرار گرفته است . (TH-RADS 3)

فالوآپ توصیه میشود.

Initial Evaluation

- Personal and family history
- Physical examination
- Thyroid function tests (TSH, FT4 if TSH abnormal)
- Neck ultrasound
- Consider disease-specific patient-reported outcome measures
- Calcitonin measurement in specific scenarios

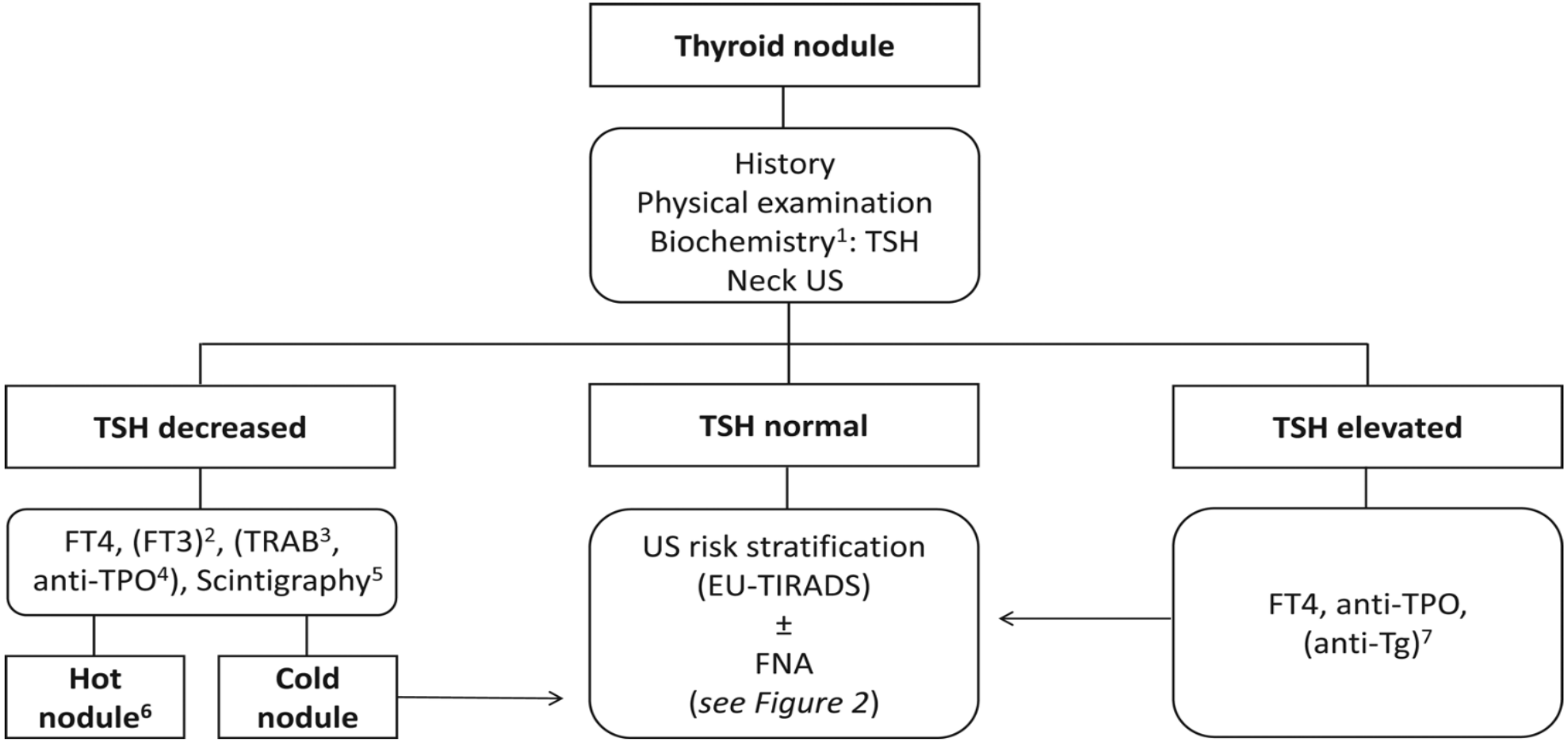


Figure 1

Initial evaluation for the investigation and diagnosis of the etiology of nodular thyroid disease. 1) Based on current evidence, the guideline panel cannot recommend for or against the routine use of calcitonin determination in the initial evaluation of a patient with thyroid nodule disease. Calcitonin determination should be considered in selected conditions (for details see the guideline text). 2) If the FT4 is normal, FT3 should be measured. 3) Based on the clinical context TSH receptor antibody determination may be considered to define the etiology of hyperthyroidism. 4) Consider TPOAb determination in case of clinical and US suspicion of thyrotoxicosis related to thyroiditis. 5) In current or previous iodine-deficient areas, the use of scintigraphy may be considered for nodular goiter and also for individuals with normal TSH. 6) See main text for management (paragraph 'Radioiodine therapy'). 7) In case of clinical or US suspicion of chronic lymphocytic thyroiditis and negative TPOAb, Tg antibody determination may be considered. EU-TIRADS, European Thyroid Imaging and Reporting Data System; FNA, fine-needle aspiration; FT3, free tri-iodothyronine; FT4, free thyroxine; Tg, thyroglobulin; TPO, thyroid peroxidase; TRAB, TSH receptor antibody; TSH, thyroid-stimulating hormone; US, ultrasound.

Thyroid Ultrasound

- Perform in all suspected nodular thyroid disease cases
- Evaluate thyroid bed, anterior neck, cervical lymph nodes
- Use EU-TIRADS for risk stratification
- Describe size, location, features of all suspicious nodules
- Consider complementary techniques (Doppler, elastography, CEUS)

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).

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.

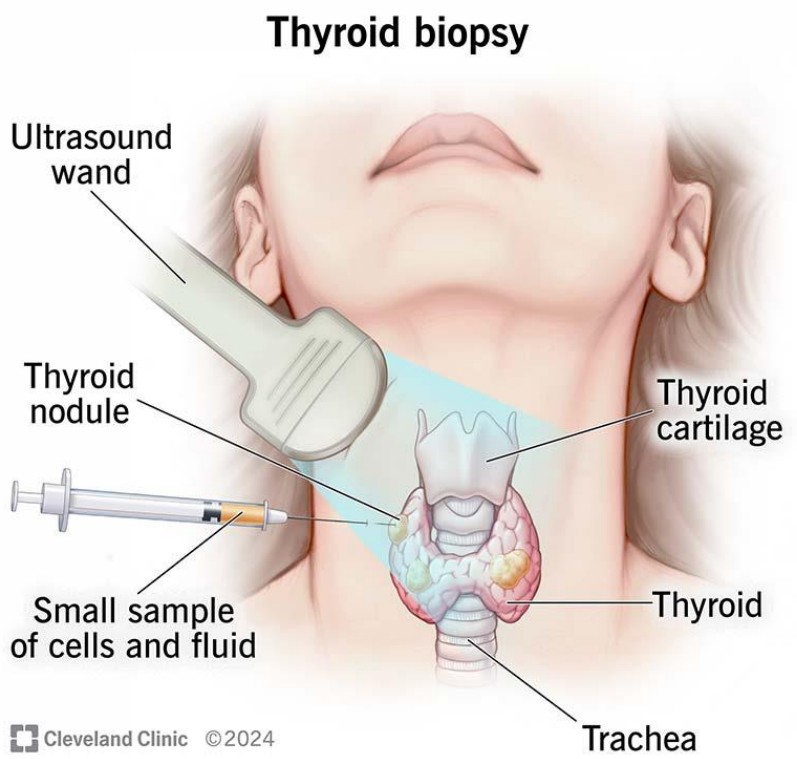
[b]FNA should be performed in nodules irrespectively of EU-TIRADS score if either pathological lymph nodes are present or the nodule is suspicious of extra-thyroidal extension.

[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.

FNA, fine-needle aspiration; TIRADS, Thyroid Imaging and Reporting Data System.

Thyroid Biopsy

- Fine-needle aspiration (FNA) is the primary biopsy method
- US-guided FNA recommended
- Indications based on EU-TIRADS category and size
- Core-needle biopsy as a second-line procedure in specific cases
- Tg/calcitonin washout for suspected lymph node metastases



Strenghts and Weaknesses of FNA

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

FDG, fluorodeoxyglucose; FNA, fine-needle aspiration; MEN2, multiple endocrine neoplasia type 2; MIBI, methoxy-isobutyl-isonitrile; MNG, multinodular goiter.

Management of Asymptomatic Nodules

- Follow-up intervals based on EU-TIRADS category and size
- EU-TIRADS 2: Re-evaluate >10 mm nodules in 3-5 years
- EU-TIRADS 3 (<20 mm): Re-evaluate 10-20 mm nodules in 3-5 years
- EU-TIRADS 4 (<15 mm): Re-evaluate in 1 year
- EU-TIRADS 5 (<10 mm): Re-evaluate every 6-12 months

Cytopathology-based Management

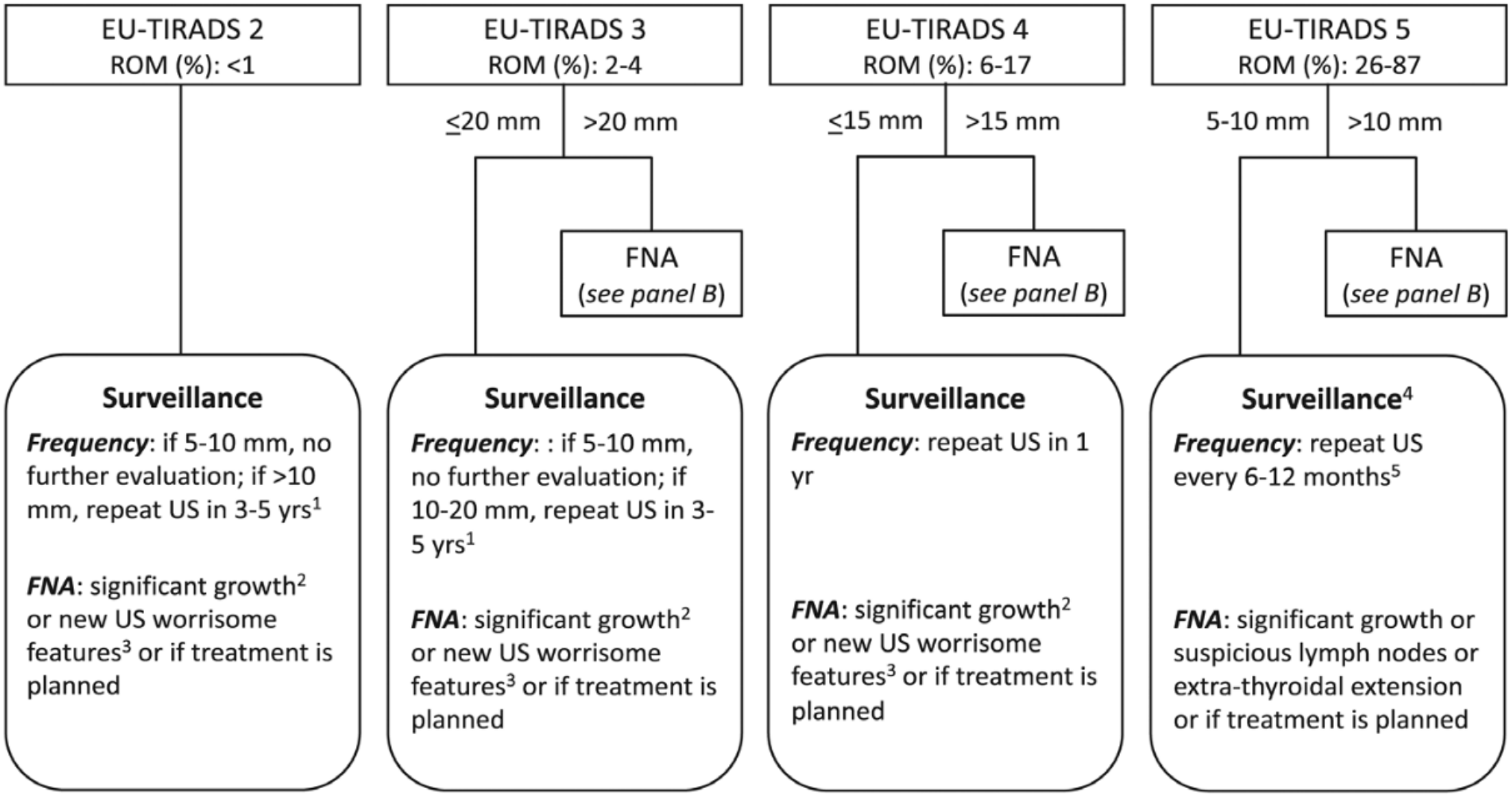
- Use Bethesda System for Reporting Thyroid Cytopathology
- Management based on Bethesda category and EU-TIRADS score
  - Bethesda I (Non-diagnostic): Repeat FNA
  - Bethesda II (Benign): Follow-up based on EU-TIRADS
  - Bethesda III (AUS/FLUS): Repeat FNA, consider molecular testing
  - Bethesda IV-VI: Consider surgery or further evaluation

Cytopathology-based Management

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, metastatic)	2–5%	97–99%

US based approach

A **1st line approach**: perform neck US and stratify the thyroid nodule risk according to EU-TIRADS



FNA+US Based approach

B **2st line approach**: perform FNA cytology

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]	**EU-TIRADS 3, 4 and 5 (*>10 mm*)** *Recommend:* ▪ *Surgery*[7]	

Molecular Diagnostics

- Consider for indeterminate cytology (Bethesda III/IV)
- Various tests available: ThyroSeq, Afirma GSC, ThyGeNEXT/ThyraMIR
- Can help identify patients most likely benign or high risk for malignancy
- Limited use outside USA due to cost and lack of long-term outcome data

Genetic diagnostics

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 ThyroSeq or ThyGeNEXT/ThyraMIR or ThyroidPrint tests, a similar problem would likely also appear for these tests.	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 potential risk of variability when the test is performed in different labs.
Caveat	Arguments that unnecessary surgeries are avoided based on NPV/BCR incorrectly assume that all indeterminate thyroid nodules would undergo diagnostic surgery in the absence of molecular testing. If each positive molecular test result triggered surgery, implementation of molecular testing would substantially increase overtreatment. For *RAS* mutations, see text ('Molecular diagnostics applied to cytology').			

CNA, copy number alteration; FNA, fine-needle aspiration; GCS, Genomic Sequencing Classifier; LOH, loss of heterozygosity; miRNA, microRNA; NGS, next-generation sequencing; NPV, negative predictive value; PCR, polymerase chain reaction; PPV, positive predictive value; ROM, risk of malignancy.

Non-ultrasound Imaging Modalities

- Thyroid scintigraphy for subnormal TSH
- Useful for detecting functioning nodules and multinodular goiter
- Limited use of CT/MRI for local extension assessment
- Consider [18F]FDG-PET/CT for indeterminate cytology in some cases

Therapeutic Options: Non-surgical Approaches

- Clinical surveillance for benign, asymptomatic nodules
- Radioactive iodine (RAI) for hyperfunctioning nodules and some multinodular goiters
- Minimally invasive techniques:
  - Ethanol ablation for cystic lesions
  - Thermal ablation for symptomatic benign solid nodules

Therapeutic Options: Surgical Approach

- Indications: symptomatic nodules, suspicious cytology, large size (≥4 cm)
- Consider patient preference and available alternatives
- Extent of surgery depends on diagnosis and disease extent
- Lobectomy for unilateral disease, near-total thyroidectomy for bilateral disease

Summary of recommendations

- ✓ Initial evaluation should include personal/family history, physical exam, thyroid function tests, and neck ultrasound.
- ✓ Neck ultrasound should assess the thyroid gland and cervical lymph nodes in all patients suspected of nodular thyroid disease.
- ✓ Use EU-TIRADS to describe nodule features and estimate malignancy risk.
- ✓ Fine-needle aspiration (FNA) indications: EU-TIRADS 5 >10 mm, EU-TIRADS 4 >15 mm, EU-TIRADS 3 >20 mm.
- ✓ Repeat FNA for non-diagnostic samples, Bethesda III cytology, discrepancies between ultrasound and cytology, and significant nodule growth.

Summary of recommendations

- ✓ For asymptomatic nodules not undergoing FNA, follow-up intervals depend on EU-TIRADS category and size.
- ✓ Correlate cytological diagnosis with clinical, ultrasound and laboratory results.
- ✓ Management of Bethesda I (non-diagnostic) depends on EU-TIRADS category; may include repeat FNA, core needle biopsy, or surgery.
- ✓ For Bethesda II (benign), re-evaluate in 3-5 years for EU-TIRADS 3-4; repeat FNA for EU-TIRADS 5.
- ✓ For Bethesda III, repeat FNA; further management depends on EU-TIRADS category.

Summary of recommendations

- ✓ For Bethesda IV, offer surgery or consider molecular testing if available.
- ✓ For Bethesda V-VI, recommend surgery; consider active surveillance for small nodules.
- ✓ Molecular testing may be considered for cytologically indeterminate nodules.
- ✓ Perform thyroid scintigraphy when TSH is subnormal to diagnose functioning nodules.
- ✓ Consider radioactive iodine for hyperfunctioning nodules and benign multinodular goiter as an alternative to surgery.

Case

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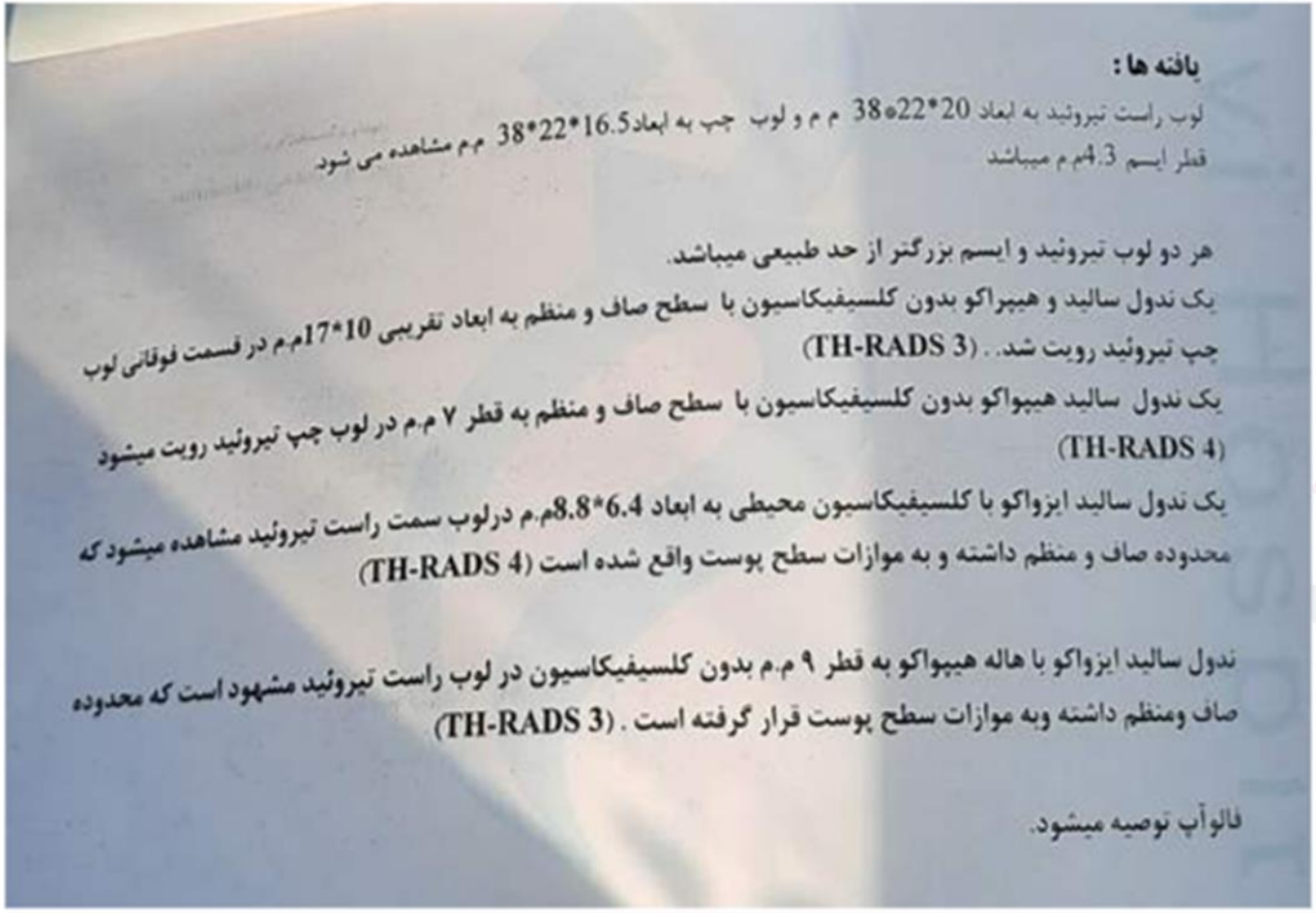

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