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Review Article

Management of Thyroid Nodules

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ABSTRACT

Thyroid nodules are common and the prevalence varies between 4 and 7% by palpation and 19–68% by high-resolution USG. Most thyroid nodules are benign, and the malignancy rate varies between 7 and 15% of patients. Thyroid nodules are detected incidentally during clinical examination or, more often, during imaging studies performed for another reason. All detected thyroid nodules should be evaluated clinically. The main test in evaluating thyroid function is thyroid stimulating hormone (TSH). If the serum TSH level is below the normal reference range, a radionuclide thyroid scan should be performed to determine whether the nodule is hyperfunctioning. If the serum TSH level is normal or high, ultrasonography (US) should be performed to evaluate the nodule. US is the most sensitive imaging method in the evaluation of thyroid nodules. Computed tomography (CT) and magnetic resonance imaging are not routinely used in the initial evaluation of thyroid nodules. There are many risk classification systems according to the USG characteristics of thyroid nodules, and the most widely used in clinical practice are the American Thyroid Association guideline and the American College of Radiology Thyroid Imaging Reporting and Data System. Fine needle aspiration biopsy (FNAB) is the gold standard method in the evaluation of nodules with indication according to USG risk class. In the cytological evaluation of FNAB, the Bethesda System for Reporting Thyroid Cytopathology (TBSRTC) is the most frequently applied cytological classification. TBSRTC is a simplified, 6-category reporting system and was updated in 2023. The application of molecular tests to FNAB specimens, especially those diagnosed with Bethesda III and IV, is increasing to reduce the need for diagnostic surgery. Especially in Bethesda III and IV nodules, different methods are applied in the treatment of nodules according to the malignancy risk of each category, these are follow-up, surgical treatment, radioactive iodine treatment, and non-surgical ablation methods.

Keywords: Imaging, risk classification, thyroid nodule, treatment management

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The prevalence of thyroid nodules is common in public population. Their prevalence varies according to the method of detection and the selected population and is 4–7% by palpation, 19–68% by high-resolution ultrasound (US) in randomly selected individuals, with a higher frequency in women and the elderly. Most of thyroid nodules are benign. However, malignancy rate varies between 7 and 15% depending on the factors associated with patients.[1]

Along with the developments in imaging methods, an increase in both the detection of thyroid nodules and, as a

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result, the detection of thyroid cancer has been remarkable in the last 3–4 decades.[2] Detection of any mass in a patient is one of the most worrisome situations that causes fear of cancer in the patient.[2,3]

It is important to evaluate all thyroid nodules to identify those that are clinically significant requiring follow-up or treatment. Detailed further evaluation and surgical intervention are not required in most nodules. The main reasons leading to surgery in thyroid nodules are presence of cancer, hyperfunctioning, and compression symptoms of a nodule. Diagnosis and treatment of thyroid nodules is one of the most controversial issues. In this section, approaches to the diagnosis and treatment of thyroid nodules will be evaluated.

Definitions

Thyroid Nodule: Thyroid nodule is defined as a lesion that can be distinguished from the surrounding thyroid parenchyma by US examination or other sensitive imaging methods.[1,4]

If the thyroid is structurally and/or functionally characterized by nodules that develop with transformation in one or more areas, it is defined as nodular goiter.[5] Nodular goiter is defined as a solitary thyroid nodule if it originates from a single nodule, and as a multinodular goiter (MNG) if there is more than one nodule.[6,7]

In US examinations performed for palpable solitary thyroid nodules, one or more extrathyroid nodules are detected except for the palpable nodule at a rate of 20–48%.[4]

In other words, solitary or multiple nodules in the thyroid may be palpable or non-palpable (Fig. 1). Knobel proposed the term nodular thyroid disease to describe all thyroid nodules, including clinically palpable and non-palpable solitary and multiple nodules, and stated that this term would be more descriptive and appropriate.[7]

In the fifth edition of the WHO classification of thyroid neoplasms published in 2022, the clinical entity known as MNG was previously used as a pathological entity; however, it was stated that this term is not appropriate as it includes many lesions such as thyroiditis, hyperplasia, or tumoral lesions.

To solve this problem, the term "thyroid follicular nodular disease" has been proposed in this edition to avoid describing a lesion as hyperplastic, neoplastic, or contradictory "adenomatous hyperplasia."[8] We think that it would be appropriate to use the term "nodular disease of the thyroid," which is recommended in both clinical and pathological classification, instead of the term thyroid nodule, due to its comprehensiveness.

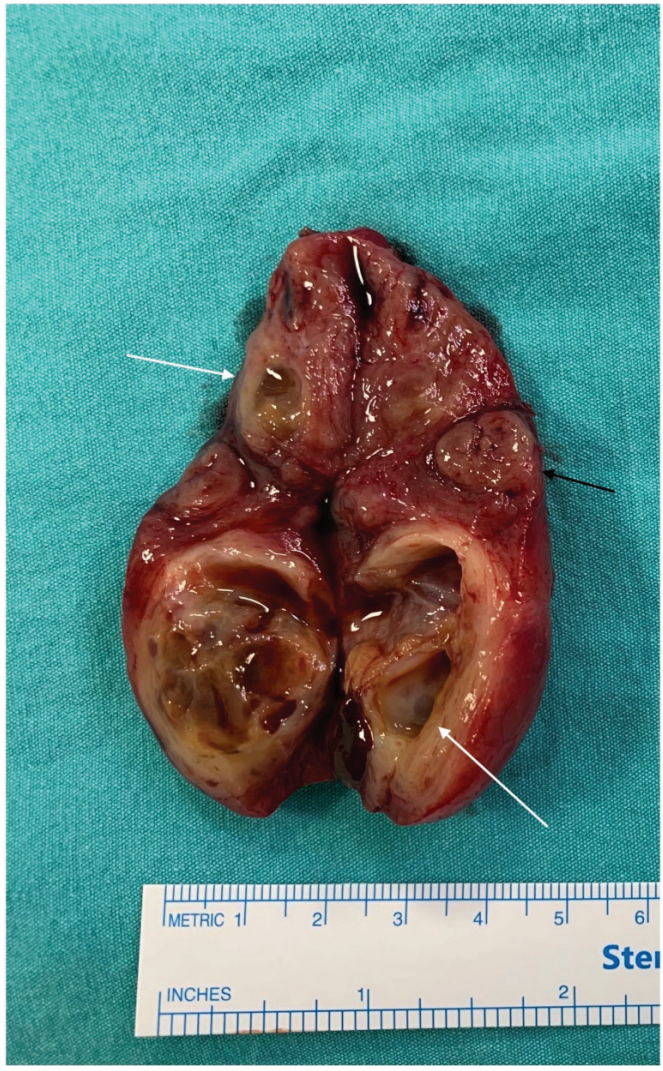

Figure 1. Multiple nodules in thyroid gland. Black arrow shows a solid nodule, white arrows show cystic thyroid nodules with septae.

Clinical Risk Factors for Thyroid Cancer

Although thyroid cancers are the most common endocrine cancer, the malignancy rate in thyroid nodules is not high. Although the etiology of many thyroid malignancies is not clear, it is known that there are some risk factors for thyroid cancer. Exposure to ionizing radiation due to treatment or accident during childhood or adolescence, effects of dietary iodine intake (increased or decreased dietary iodine intake), family history of thyroid cancer, and hereditary syndromes associated with thyroid cancer are these risk factors. Although genetic changes and genotype phenotype relationship in familial medullary cancers are well known, genetic factors in non-medullary thyroid cancers (non-MTC) have not been fully revealed. Family history of non-MTC increases the risk of malignancy (RoM) 5–10 times.[2,9]

Familial non-MTC can be divided into two different groups as syndromic and non-syndromic cancers; and most of these cancers are not associated with syndromes. Syndromes associated with non-MTC; familial adenomatous polyposis and Gartner syndrome (both cribriform pattern papillary thyroid cancer [PTC]), Carney complex (PTC and Follicular thyroid cancer [FTC]), Cowden syndrome (PTC [Classic and follicular variant] FTC), DICER 1 syndrome (differentiated thyroid cancer [DTC]), Werner syndrome (PTC, FTC, Anaplastic thyroid cancer [ATC]), PTEN hamartoma tumor syndrome (FTC, PTC, follicular variant PTC, MNG); rarer syndromes associated with non-MTC are Peutz- Jeghers syndrome (PTC, DTC), Pendred syndrome (PTC, FTC, ATC), Li-Fraumeni syndrome (PTC classic, follicular variant), ataxia telangiectasia syndrome (PTC), papillary renal neoplasia (PTC), and McCune-Albright syndrome.[9]

Familial MTCs are familial MTC and multiple endocrine neoplasia 2A/2B syndromes.[10,11] Recently, the intraglandular localization of the nodule has been demonstrated to be an independent risk factor for malignancy. Nodules arising from the isthmus show the highest risk for cancer diagnosis; whereas those in the lower third of the lobe have the lowest risk compared to those in the middle or upper pole of the lobe.[12]

The age at which the thyroid nodule is detected in a patient affects the cancer risk of the nodule; younger (<14) and older (>70) age are associated with a higher RoM.[4]

Gender of the patient is another important factor for malignancy risk in thyroid nodule. Cancer development risk in female gender is approximately 3 times higher than male gender. The effect of hormonal factors that may explain the mechanism of this risk factor is not clearly known.[2] However, the RoM is higher in male patients with thyroid nodules.[13]

Ethiology and Pathogenesis

Many benign and malignant diseases can cause thyroid nodules. Benign thyroid diseases that cause the most of thyroid nodules are follicular nodular disease of the thyroid, follicular adenoma, oncocytic adenoma, simple or hemorrhagic cyst, Hashimoto's thyroiditis, and subacute thyroiditis.[8,14] Non-invasive follicular thyroid neoplasm with papillary-like nuclear features, thyroid tumors of uncertain malignant potential, and hyalenized trabecular tumor are classified as low-risk tumors (Low-risk neoplasms) and these tumors also rarely present as nodules.[8]

Follicular cell-derived tumors constitute the majority of primary malignant thyroid tumors presenting with a thyroid nodule; PTC, invasive encapsulated follicular variant papillary carcinoma, FTC, oncocytic carcinoma of the thyroid, follicular-derived carcinomas, high-grade, and ATCs. Parafollicular C cell-derived MTCs are less frequently tumors that play a role in the etiopathogenesis.

Sometimes lymphomas and metastatic cancers may involve the thyroid and present as a nodule. Rarely, malignant or benign nodular growths may occur from the connective and supporting tissue surrounding the thyroid follicles.[8]

Clinical Diagnostic Approach in Thyroid Nodules

Thyroid nodules detected both clinically and incidentally on imaging performed for other reasons should be evaluated regarding the cancer risk, presence of hyperfunctioning, compression symptoms and signs by history, physical examination, biochemical tests, and imaging modalities (Figs. 2 and 3).[15,16]

In present, with the widespread use of imaging methods, most of the thyroid nodules are detected incidentally and these nodules are typically not palpable. Incidentally detected thyroid nodule rate is 20–67% in extrathyroidal US examinations (evaluation of carotid artery, parathyroid,

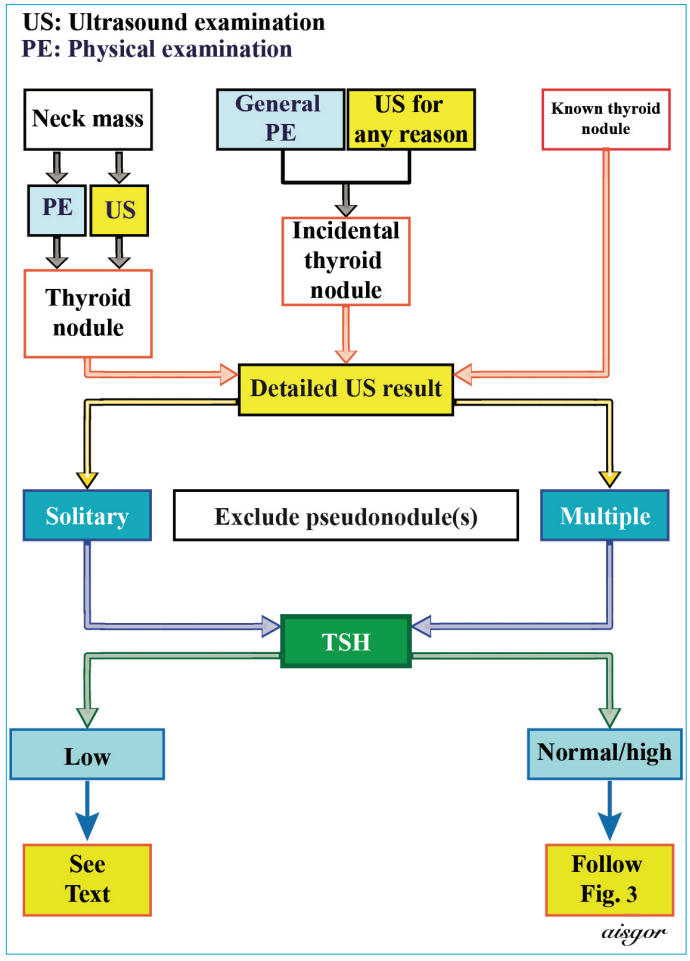

Figure 2. Clinical algorithm for evaluation of thyroid nodules (US: Ultrasound examination, PE: Physical examination, TSH: Thyroid-stimulating hormone).

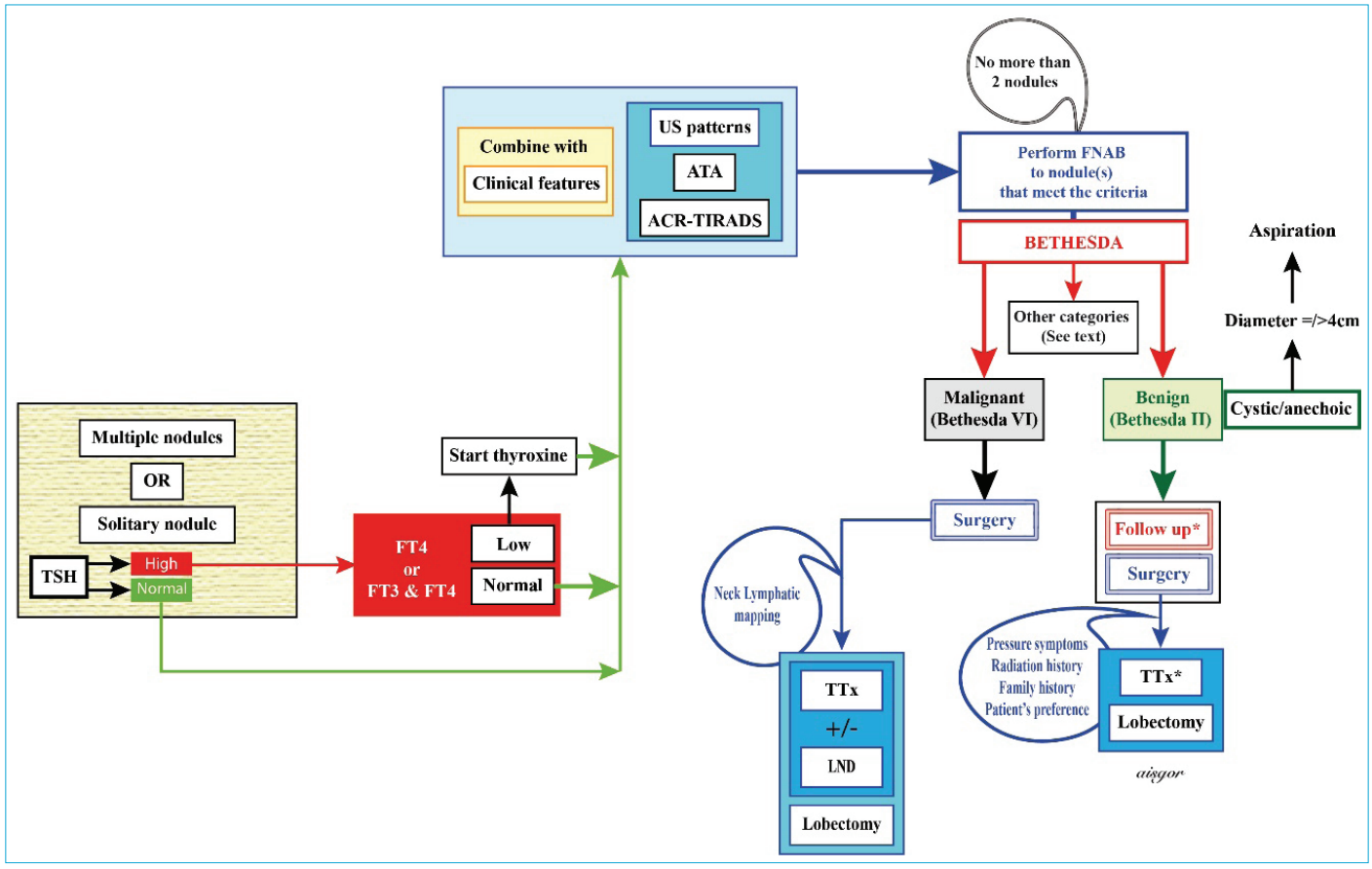

Figure 3. Clinical algorithm for thyroid nodules with patients who have high or normal Thyroid-stimulating Hormone levels.

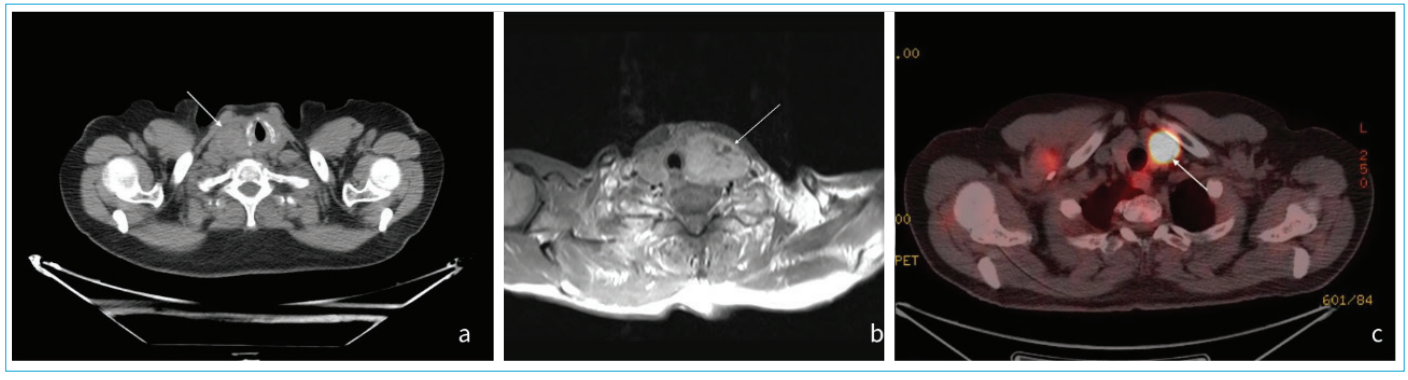

Figure 4. (a) An incidental thyroid nodule (white arrow) causing tracheal deviation in computed tomography scan. (b) An incidental thyroid nodule (white arrow) causing tracheal deviation in T1-weighted image in magnetic resonance imaging. (c) An incidental thyroid nodule (white arrow) with increased 18-Fluoro-Deoxyglucose (FDG) uptake in FDG-Positron Emission Tomography/Computed Tomography.

cervical lymph node, internal jugular vein and other structures of the neck), 9–25% in computerized tomography (CT) (Fig. 4a) and magnetic resonance imaging (MRI) (Fig. 4b), and 1–4.3% in positron emission tomography/computed tomography (PET/CT) (Fig. 4c).

Especially in PET/CT performed with 18-fluorodeoxyglucose (FDG), the RoM is high in active nodules and can reach 30%. Incidental thyroid nodules can also be detected in other nuclear medicine imaging studies. In small studies, especially in scintigraphies with technetium-99m methoxyisobutilisonitrile (MIBI), the malignancy rate in MIBI-enhancing thyroid nodules is 22–66%, and in PET/CT with radio-labeled prostate-specific membrane antigen (PSMA), the malignancy rate is 26% in PSMA-enhancing thyroid nodules. The RoM in incidental nodules detected on MR and CT varies between 0 and 11% (17). In addition to these, additional nodules are detected at a rate of 20–48%

in patients undergoing USG for palpable thyroid nodules.[4] These nodules detected other than palpable nodules can also be considered as incidental thyroid nodules.[17]

Patient's History, Symptoms, and Clinical Findings

Although patient history and physical examination alone cannot determine the nature and composition of the thyroid nodule, there are some clinical features that may cause suspicion of malignancy.[18] The risk factors listed above for malignancy such as history of familial thyroid cancer or syndroms related to thyroid cancer, and radiation to head and neck should be evaluated. The patient's age and gender should be considered in the risk assessment for malignancy.[19]

Patients may range from asymptomatic to patients exhibiting symptoms of compression, hyperthyroidism, or hypothyroidism. Symptoms may develop depending on the size and function of the nodules, or the total volume and location of the thyroid gland.[20] In symptomatic patients, a detailed history and complete physical examination can guide the selection of appropriate clinical and laboratory investigations.[21,22] Furthermore, in symptomatic patients; the duration of complaints, whether they have been evaluated before or are under follow-up, and growth or any changes in nodule should be evaluated.[19] Local symptoms do not occur in most of thyroid malignancies which rarely develop compression symptoms, vocal cord paralysis, or esophagus symptoms.[23] Compression-related symptoms and signs such as cough and dysphonia may also suggest the risk of an underlying malignant lesion. Therefore, surgical treatment should be considered in patients with an enlarged thyroid mass and vocal cord paresis, although cytological results are not compatible with malignancy.[23-25] The growth rate in the size of a nodule is not a reliable feature in distinguishing between benign and malignant nodules.[26] In benign nodules, slow growth can be seen over the years.[21,22] Progressive nodule growth seen within weeks or months in a stable or recently noticed nodule may suggest malignancy.[23,24] The appearance of a sudden development of swelling in the thyroid region accompanied by pain is usually due to bleeding from the cystic nodule.[27] However, in the case of progressive and painful enlargement of the thyroid nodule in patients; anaplastic thyroid carcinoma, rare forms of chronic thyroiditis (e.g., Riedel's disease), and primary lymphoma should be considered.[23,24]

Despite the low predictive value of palpation, careful examination, and palpation of the thyroid gland, anterior and lateral lymph node compartments should be performed.[4] The presence of solid, firm nodules fixed to surrounding structures such as trachea and strep muscles, enlarged regional lymph nodes, or vocal cord paralysis by palpation increases the RoM over 70%.[18]

Laboratory Examination

Symptomatology and physical examination findings are not sufficient for the evaluation of thyroid function, and biochemical evaluation should also be performed for the diagnosis. The main test giving information about the function of the thyroid gland is the serum thyroid stimulating hormone (TSH) level. TSH measurement should be performed first in all patients suspected of having a thyroid nodule (Fig. 2). Normal serum TSH level indicates that the function of the thyroid gland is normal in almost all patients.[28,29]

TSH measurement is usually sufficient in the evaluation of many patients with thyroid nodules, most tests other than TSH are not necessary. If the serum TSH level is below the normal reference range, a radionuclide thyroid scan should be performed to determine whether the nodule is hyperfunctional (Fig. 2). If the serum TSH level is normal or high, radionuclide scanning should not be performed as the initial imaging evaluation (Fig. 3).[1,23]

Since hyperfunctional nodules rarely contain malignancy, cytological evaluation is not necessary. If there is overt or subclinical hyperthyroidism, additional evaluation is necessary. High serum TSH level is associated with an increased RoM in the thyroid nodule, as well as with more advanced thyroid cancer.[1]

If the TSH level is outside the reference range (high or low); free T4 (fT4), total T3 or free T3 (fT3), and thyroid antibodies such as antithyroid peroxidase antibody (anti-TPO), antithyroglobulin antibody (anti-Tg), TSH receptor antibody (TSHRab) can be examined for the confirmation of thyroid dysfunction and diagnosis of the disease, respectively.[28,29]

Thyroglobulin Measurement: Although serum thyroglobulin (Tg) levels are typically high in unoperated thyroid cancer patients, they can also be markedly elevated in patients with benign MNG.[30-32]

Tg is a biomarker that is frequently used in the monitoring of recurrence in patients with thyroidectomized for follicle cell-derived thyroid cancer. However, thyroglobulin (Tg) measurement is not recommended routinely in the evaluation of thyroid nodules, as serum Tg levels are insensitive and nonspecific for thyroid cancer.[1]

Calsitonin Measurement: Calcitonin is a sensitive and specific biomarker used in the diagnosis and follow-up of parafollicular C cell-derived MTC. In addition, MTC is a rare form and its incidence in thyroid nodules is 0.14–0.4%.[33,34]

Routine measurement of calcitonin in the evaluation of thyroid nodules is controversial.[35] Serum calcitonin measurement is recommended in selected patients with nodules who have a family history and clinical suspicion of

familial MTC. In addition, calcitonin level should be measured when MTC is suspected in US findings or uncertain cytology.[4]

Imaging Methods

Thyroid Ultrasonography (US)

High-resolution US is the most sensitive method available and superior to other imaging methods in detecting thyroid nodules, measuring the size of the nodule, determining its shape, borders, localization and number, echogenicity, content, and evaluate any associated changes in the thyroid gland.[28] It is a non-invasive, inexpensive, and ionizing radiation-free imaging method, and it is important that it should be performed by experienced physicians. Cervical lymph node examination with US should be performed in all patients with or suspected of having a thyroid nodule. [1,28]

Sonographic features; thyroid parenchyma (homogeneous or heterogeneous) and gland size; the size (in three dimensions) and location of the nodule (e.g., right upper lobe), as well as the composition of the nodule (solid, cystic, or spongiform), echogenicity (hypoechoic, isoechoic, hyperechoic, and heterogeneous), marginal features, presence and type of calcifications, shape (wider than tall or taller than wide), and vascularity of nodule should be included in US report (Fig. 5 and Table 1) The size, shape, localization, echogenicity, vascular pattern, calcification, and/or cystic change of cervical lymph nodes should be specified if there is (Fig. 6).[18]

The pattern of sonographic features associated with the nodule indicates the RoM and, combined with the nodule size, guides the decision-making process for fine needle aspiration biopsy (FNAB).[36,37]

Should US be Performed in a Toxic Nodule?

In the patient group with low serum TSH levels and nodules detected on thyroid scintigraphy, US should be performed to evaluate both the presence of nodules that do not require FNAB compatible with hyperfunctional areas on scintigraphy and other non-functional nodules that meet the sonographic criteria for FNAB.[38] Since the malignancy rate is low in hyperactive nodules on scintigraphy, it is suggested that FNAB and cytological evaluation are not necessary.[1] However, this proposal is still a controversial issue in the literature. In a recent meta-analysis, Lau et al. [39] reported that although the malignancy rate was reduced by 55% in hot nodules, it was not zero and the incidence was higher than expected. In another recent study by Rosario et al., [40] although the malignancy rate is lower than that of the non-autonomous nodules, it is 14.6% in nodules with autonomous function. Researchers recommend performing FNAB in autonomous nodules larger

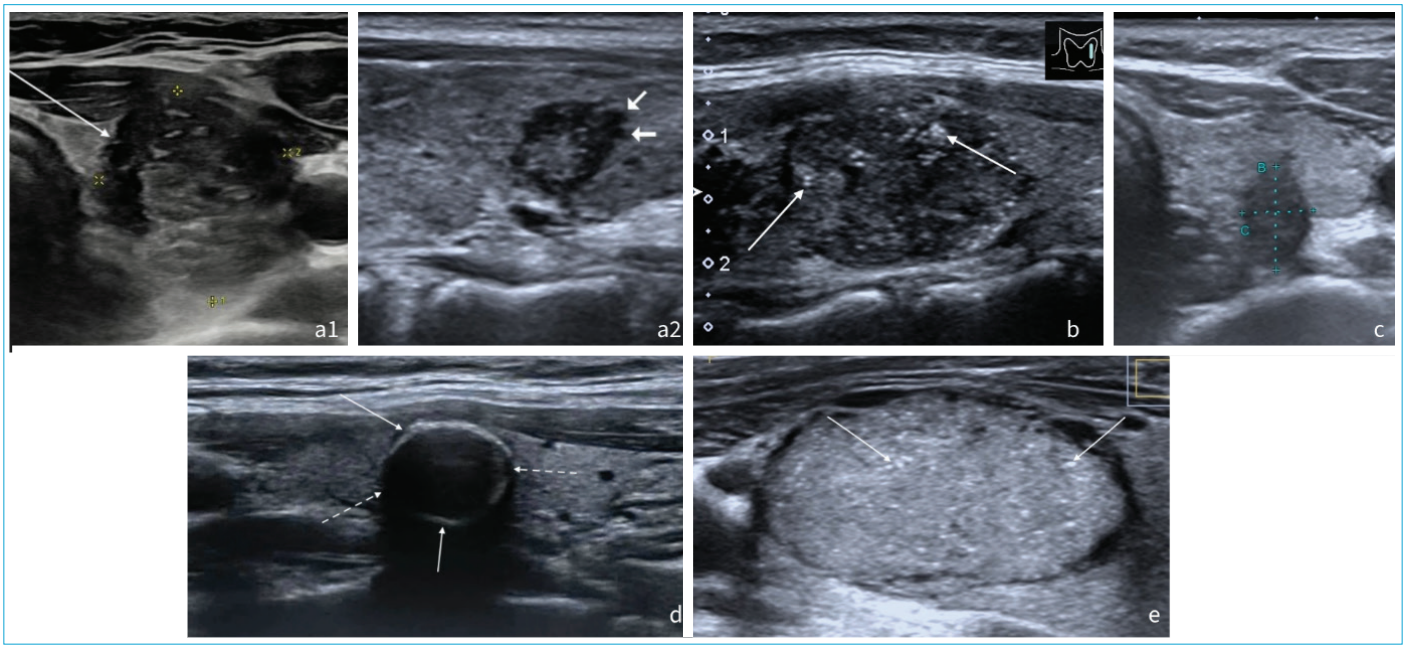

Figure 5. (a1): A taller-than-wide and markedly hypoechoic thyroid nodule (white arrow) with irregular margin and punctate echogenic foci on background parenchyma. (a2): A thyroid nodule with irregular margin (white arrows). Post-operative pathology result was papillary carcinoma on autoimmune thyroiditis background. (b): A hypoechoic thyroid nodule with punctate echogenic foci (White arrows). (c): A thyroid nodule with taller-than-wide shape. (d): A thyroid nodule showing rim calcification (White continuous arrows show calcified margins and white dashed arrows show non-calcified margins) (e): A hyperechoic thyroid nodule with multiple punctate echogenic foci (White arrows).

Table 1. Comparison of ATA and ACR TI-RADS systems

VARIABLES THAT SHOULD BE INCLUDED IN THE THYROID US REPORT			
Thyroid	Dimensions, volume, vascularity	Lymph node(s)	Neck level
Nodule	Dimensions*, shape		Dimensions, shape
	Location, composition (includes echogenicity)		Cortical thickness, echogenicity
	Margins		Calcifications / cystic areas
	Calcifications: macro/micro/peripheral		Soft tissue relationship
	Vascularity		Vascular patern

CLASSIFICATIONS							
ATA			ACR TI-RADS				
Group	US PATTERNS	ROM (%)	Group	TIRADS (TR) Class	Total Score	US PATTERNS	Point
Benign	Pure cystic (no solid component)	< 1	**Benign**	**TR 1**	**0**	**COMPOSITION (Choose one)**	
						Spongiform	0
						Cystic[1]	0
						Mixed[2]	1
						Solid	2
						Cannot be determined[3]	2
Very Low Risk	Spongiform	< 3				**ECHOGENITY[4] (Choose one)**	
	Partially cystic					Anechoic	0
	Without features consistent with the following groups					Iso/hyper echoic	1
						Hypoechoic	2
						Very hypoechoic	3
Low Risk	Iso / hyperechoic solid	5-10	**Not Suspicious**	**TR 2**	**2**	**SHAPE: Diameter[5] Choose one**	
	Cystic + eccentric solid area					Wider than tall	0
	Wider than tall[5]					Taller than wide	3
	No Microcalcifications		**Mildly Suspicious**	**TR 3**	**3**	**MARGIN Choose one**	
	No Irregular margin					Smooth	0
	No ETE					Ill-defined	0
Intermediate Risk	Hypoechoic solid	10-20	**Moderately Suspicious**	**TR 4**	**4-6**	Lobulated[6] / irregular[7]	2
	Smooth margins					ETE	3
	Wider than tall [5]						
	No ETE						
	No Microcalcifications						
High Risk	Hypoechoic solid Partially cystic+ Hypoechoic solid areas **PLUS one or more features** - Irregular margin [7] (infiltrative, microlobulated) - Microcalcifications - Rim Calcifications[10] - Taller than wide[5] - ETE	% 70-90	**Highly Suspicious**	**TR 5**	**≥ 7**	**ECHOGENIC FOCI Choose all that apply**	
						None	0
						Comet like artifact[8]	0
						Macrocalcification[9]	1
						Rim calcification[10]	2
						Small echogenic foci (microcalcification)	3

1: More than 50% of the spongiform nodule contains small cystic areas. 2: Mixed: Contains cystic and solid areas. The component that occupies more than 50% of the nodule determines the type of nodule. 3: If the composition of the nodule cannot be determined due to dense calcifications, 2 points. are given. 4: Hypoechoic nodule: If nodule echogenicity is lower than that of intact thyroid parenchyma; very hypoechoic nodule: If nodule echogenicity is lower than that of strap muscle. 1 point is given for a nodule whose echogenicity cannot be determined exactly. 5: When the ultrasound probe is held in the transverse plane, the measurement parallel to the direction of the sound waves (beam) is recorded as depth (tallness!) or antero-posterior diameter, and the measurement perpendicular to the sound waves is recorded as width. 6: Lobulation: Protrusion into adjacent tissue. 7: Irregular margin: It is defined as the margin of the nodule being rough or having spiky protrusions or sharp corners. 8: A "V"-shaped flare, usually greater than 1 mm, in the cystic component of the nodule is defined as a comet-like appearance. 9: Macrocalcification: Coarse calcification causing acoustic shadowing. 10: Complete (eggshell-like) or incoplete thin calcifications along margin of the nodule, and may cause acoustic shadowing.)(Table 1 is established using the ATA and ACR TI-RADS guidelines (1,4)

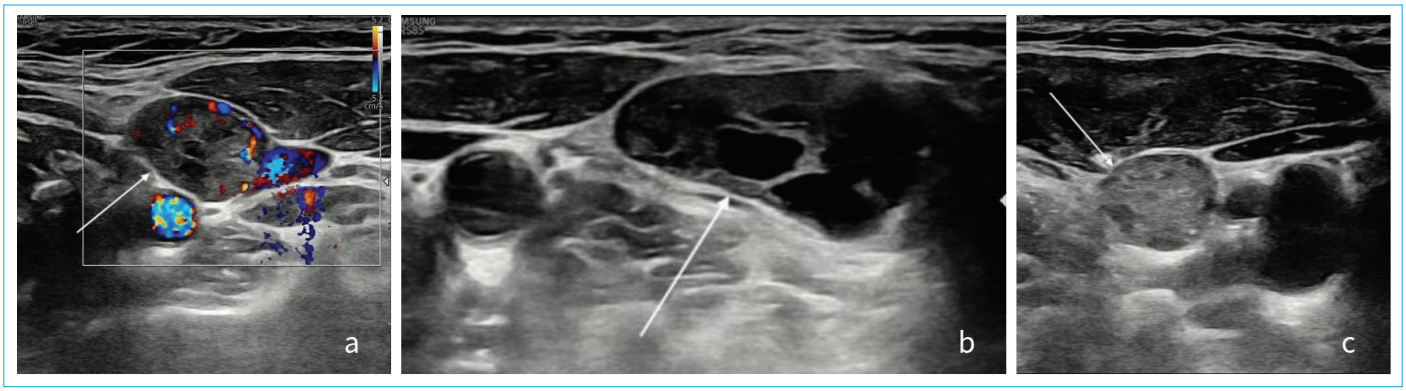

Figure 6. (a) A hypoechoic metastatic cervical lymph node (white arrow) with peripheric penetrating vascular structures. (b) A metastatic cervical lymph node (white arrow) with cystic components. (c) A hyperechoic metastatic cervical lymph node (white arrow).

than 1 cm with ultrasonographic findings suspicious for malignancy. FNAB is also recommended in other studies in selected patients particularly with suspicious features on US in autonomous functioning nodules.[41-43] Although there is still a need for extensive studies on this subject, it strengthens the idea that suspicious US features of the hyperfunctional nodule should be taken into account in terms of malignancy and FNAB should be performed in selected patients.

Ultrasonographic Risk Classification

Multiple risk classification systems based on the above-mentioned sonographic features of thyroid nodules have been established to develop a common language for identifying and classifying the nodules at greatest risk for morbidity, and preventing unnecessary biopsies performed on benign nodules (Table 1).[1,4,26,44-48]

Risk classification systems are used for dividing thyroid nodules into categories based on their composite sonographic features associated with malignancy risk and this classification can guide surveillance strategies and performing US-guided FNAB. One of the two most widely used systems in clinical practice is the American College of Radiology Thyroid Imaging Reporting and Data System (ACR TI-RADS) used by many radiologists, and the other is the American Thyroid Association (ATA) guidelines used by many endocrinologists (Table 1). ACR TI-RADS sums it up by assigning points for each of the five ultrasound characteristics and identifies risk categories from TR1 (benign) to TR5 (highly suspicious). In the ATA guideline, the US features were combined and the nodules were divided into five categories as highly suspicious, moderately suspicious, low suspicious, very low suspicious, and benign patterns. Biopsy and follow-up criteria according to ATA and ACR TI-RADS are summarized in Table 2. In all guidelines, FNAB is recommended considering the nodule size and RoM in the categories to avoid unnecessary biopsies.

In the ATA guideline, biopsy is recommended for nodules of >1 cm in moderately and highly suspicious nodules, and >1.5 cm with low risk. In very low-risk nodules, biopsy is recommended for nodules of > 2 cm, and it is stated that nodules of <2 cm can be followed without biopsy. Biopsy is not recommended for nodules with benign patterns (Table 2).[1,26]

In the ATA guideline, irregular margins (infiltrative and microlobulated), microcalcifications, taller than wide shape, rim calcifications with small extrusive soft-tissue component, and evidence of ETE are listed as suspicious features in US (Fig. 5 and Table 1). Solid hypoechoic or partial cystic nodules with solid hypoechoic component containing one or more of these features are categorized as highly suspicious. However, solid or partial cystic hyper/isoechoic nodules containing one or more of these features are not categorized.

In a meta-analysis of 16 studies including 21,000 nodules which have not been categorized in the ATA guideline, the pooled prevalence was 7.8% (1872 nodules; [confidence interval; CI 5.1–11.1]), with a pooled RoM 20.3% (CI 13.0–28.7), which was found to be comparable with the nodules of intermediate suspicious risk category in the ATA guideline. However, there was significant heterogeneity between studies (I2=92.8%, p<0.001); a significant difference was found between single center and multicentric studies (24.8% vs. 12.3%, respectively, p=0.031) and also between retrospective and prospective studies (25.1% vs. 8.5%, respectively, p=0.003).[49]

In the ACR TI-RADS classification, the composition, echogenicity, shape, border features, and echogenic foci of the nodule were scored on US and divided into five categories according to the sum of these scores (Table 1). Nodules not categorized by ATA are categorized by ACR TI-RADS (TR) with this scoring system. In addition, FNAB recommended nodule diameter is larger in ACR TI-RADS than that is in the

Table 2. Comparison of recommendations for follow-up and biopsy timing in ATA and ACR TI-RADS classifications

ATA			First FNA: Benign		ACR TI-RADS		
GROUP	**Recommendation for FNAB**	**Follow-up with US**			**Follow-up with US**	**Recommendation for FNAB**	**CLASS**
Benign	Not recommended (Diameter ≥ 4cm aspiration)	No routine follow up	*		No routine follow-up	Not recommended	TR 1 Benign
Very low risk	Diameter ≥ 2cm FNAB or follow	Diameter ≥ 1cm After 2 years	[1]If FNAB was performed, if there is growth[2]/change consider FNA				
		< 1cm No routine Follow up					
Low risk	Diameter ≥ 1.5cm FNAB	12–24 month intervals	if there is growth[2]/change in the nodule consider FNA		No routine Follow up	Not recommended	TR 2 Not Suspicious
					After 2 years		
					Diameter ≥ 1.5cm In 1–2 & 5 years	Diameter ≥ 2.5cm FNAB	TR 3 Mildly Suspicious
Intermediate Risk	Diameter ≥ 1cm FNAB	12–24 months at intervals			Diameter > 1 cm In 1-2-3 & 5. years	Diameter ≥1.5 cm FNAB	TR 4 Moderately Suspicious
High Risk	Diameter ≥ 1cm FNAB		US and FNAB In 12 months	Annual			
	Diameter < 1cm Follow	within 12 months			[3]Diameter > 0.5cm 6-12 months interval for 5 years	Diameter ≥ 1cm FNAB	TR 5 Highly Suspicious

*: Since there is no need for biopsy in these nodules after the first ultrasound, it can be decided whether to follow up according to clinical findings. 1: While ATA recommends FNAB for nodules ≥ 2 cm in diameter in very low risk group, ACR TI-RADS does not recommend FNAB or even follow-up with US for TR 1 and TR 2 corresponding to this class. 2: A 50% increase in nodule volume or 20% increase in 2 dimensions of the nodule in 12-18 months is considered as nodule enlargement (growth) 3: FNAB can be performed in nodules with a diameter of 0.5-1 cm, taking into account the history of exposure to ionizing radiation, a strong family history of thyroid cancer, suspicion of lymph node/distant metastasis, or the patient's preference.) (Table 2 is established using the ATA and ACR TI-RADS guidelines (1,4).

ATA guideline. TR1 (0 points) is categorized as benign, TR2 as not suspicious, and biopsy is not recommended in these nodules. FNAB is recommended in TR3- mildly suspicious (3 points) nodule of ≥2.5 cm, TR4- moderately suspicious (4–6 points) nodule of ≥1.5 cm, and TR5-highly suspicious (≥7 points) nodule of ≥1 cm.[26]

Although the malignancy risk ratios are given in the ATA guideline table, the malignancy risks are not given in the ACR TI-RADS table (Table 1). Different rates can be seen in various studies in the literature. In the literature, malignancy rates of <2% in ACR TI-RADS TR1 and TR2, 2.1–5% in TR3, 5–20% in TR4, and >20% in TR5 are noteworthy.[19]

Intranodular Vascularity

Although intranodular vascularity has been identified as a risk factor for malignancy in previous studies, it was reported that it was not a predictive factor for malignancy in subsequent studies.[50-52]

In the meta-analysis by Khadra et al., [53] there was no significant difference between benign and malignant nodules in terms of vascular flow, peripheral vascular flow, and internal vascularity in color Doppler US. It is stated that increased nodular vascularity cannot predict malignancy.

Intranodular vascularity is more common in follicular variant papillary carcinoma and follicular carcinoma compared to classic papillary thyroid carcinoma. It is depicted that intranodular vascularity is also common in medullary thyroid carcinoma.[52,54]

Color Doppler or power Doppler US is widely used to determine vascular flow in thyroid nodules, but new methods have been developed recently to evaluate vascular flow

because it is a nonspecific feature for malignancy and not of high diagnostic value. Superb microvascular imaging (SMI), one of which views low-velocity blood flow, has been started to be used in clinical practice for evaluating thyroid nodules after liver and breast. In the last metaanalysis; for malignant thyroid nodules, SMI was found superior to color Doppler US in providing significantly more information about vascularity and its diagnostic efficiency was found to be better than color Doppler US. It has been concluded that SMI had better clinical application value.[55]

Another developing technique is contrast-enhanced US which was firstly used for imaging liver lesions. Afterward, it has been used for imaging the thyroid and many organs. Angiogenesis is the basis of neoplastic growth, and contrast-enhanced ultrasound (CEUS) is considered an effective technique to assess microvascularization.[56] In a recent meta-analysis, the sensitivity of CEUS was found slightly higher than that of conventional US in distinguishing between benign and malignant nodules (0.87; [95% CI: 0.82–0.90] vs. 0.84 [95% CI: 0.75–0.90]).[57] The perfusion type of CEUS has good diagnostic performance for cervical lymph node metastasis in PTC.[58]

Some features of CEUS overlap in the differentiation of malignant and benign nodules, and further studies are needed for reliable standardization.[59]

Elastography

Clinically firm thyroid nodule is associated with malignancy risk. Elastography is a dynamic technique evaluating tissue elasticity through US. At present, two different techniques are used for elastography during real-time US evaluation of palpable and non-palpable thyroid nodules. Strain elastography evaluates the degree of deformation in the tissue due to the pressure applied with the US probe. A special software evaluates the degree of displacement of the tissue under compression, and this parameter is reflected on a colored scale according to the stiffness of the nodular and extranodular tissue. The other is shear wave speed measurement, which measures the speed of shear waves propagating perpendicular to the direction of tissue displacement. The speed of shear waves is generally higher in malignant thyroid nodules than in benign nodules.[60] While elastography shows promise as a technique for noninvasive assessment of cancer risk, its performance is highly variable and operator-dependent. It is also not a standardized method for data reporting. Moreover, cystic lesions, nodules with microcalcifications, MNGs with deep-seated coalescent nodules, microcarcinomas, and nodules in chronic thyroiditis are less suitable for elastographic evaluation.[61] In the last meta-analysis, it was stated that diagnostic value of elastography in malignant thyroid nodules is limited. It should not be used completely instead of US, but it can be used as a complementary method to US and may contribute to reduce unnecessary FNAB.[62]

Thyroid US Findings in Non-PTCs

The suspicious US findings such as taller than wide shape, microcalcifications, and hypoechogenicity are well-predictive factors for papillary thyroid carcinoma but less frequently associated with other thyroid cancers.[18]

In general, US features of FTC are different from classical PTC. Tumors associated with FTC are more likely to have intranodular vascularity, iso or hyperechogenic composition, absence of calcifications on sonography, and nodules with regular margins and round shape (width greater than AP diameter). The US image in follicular variant PTC has the same US features as FTC rather than PTC. Since distant metastases are rare in folliculary cancers smaller than 2 cm, the diameter cutoff for FNAB is higher for the hypoechoic nodules.[1]

The tall cell variant of PTC usually shows the classic signs of malignancy on US including significantly hypoechoic nodules with lobulated contours and microcalcifications. Lymph node metastasis and extrathyroidal extension may be evident.

The diffuse sclerosing variant of PTC may pose a diagnostic challenge on US examination, as the gland may appear enlarged and widely hypoechoic, as in Hashimoto's thyroiditis. Numerous fine and scattered hyperechoic microcalcifications might be visualized as a "starry night" appearance in wide areas of the thyroid.[4]

Oncocytic cell neoplasms have a heterogeneous US appearance; echogenicity is usually reduced, but hyperechoic tumors are not uncommon. Vascular organization is variable. A large, irregularly circumscribed, and inhomogeneous solid structure surrounded by an irregularly thickened halo is common in these tumors.[4]

US findings of MTC are variable. Although they show US features similar to PTC such as marked hypoechogenicity and coarse calcifications, they are more likely to be rounded (not long, but wide), have regular borders, mixed echogenicity, and intranodular vascularity than PTC.[54,63,64]

Examination of Lymph Node

Evaluation of central and lateral compartments of the neck with US in terms of lymph node metastases is important. Suspicious non-palpable lymph nodes detected on US increase the RoM in the nodule and may affect the surgical plan.[18]

There is no single sensitive sonographic feature for detecting metastatic lymph nodes in thyroid cancer. Enlargement of lymph node, loss of fatty hilum, rounded shape rather than oval, hyperechogenity, cystic transformation, calcifi-

cations, and peripheral vascularity are abnormal US findings that suggest metastatic lymph nodes (Fig. 6).[1]

Artificial intelligence studies, which are also being evaluated in medicine recently, are promising to improve thyroid cancer risk estimation. Future studies using artificial intelligence should focus on improving patient outcomes and use rigorous scientific methods.[13]

Other Cross-sectional Imaging Methods

Computed Tomography (CT) and Magnetic Resonance Imaging (MRI)

CT and MRI have no routine use in the initial evaluation of thyroid nodules and do not have reliable findings for the differentiation of benign and malignant thyroid nodules. In case of situations such as the need of thyroid volume evaluation, compression on the trachea, retrosternal extension of the nodular goiter and evaluation of its relation to other intrathoracic vascular structures, prediction of invasion to surrounding tissues, and presence of conglomerate lymph node metastasis or pathological lymph node that cannot be detected through US; CT and MRI should be performed in addition to US (Fig. 4a and b).[4,20]

Iodinated contrast material is used in CT and its use should be avoided since it may cause Jod-Basedow phenomenon. In centers where nodular goiter is evaluated, the role of MRI in evaluating the volume and characteristics of nodules is limited. There are no comparative studies with reliable results regarding the use of MRI and CT methods.[7]

18-FDG-PET/CT

FDG-PET/CT has no place in the initial evaluation of a thyroid nodule.[17] Many DTC and MTCs do not uptake FDG. Therefore, PET/CT can be considered only in the pre-operative staging of aggressive malignant nodules (Fig. 4c).[4]

Scintigraphic Methods

If TSH value is below the lower limit of normal range in laboratory evaluation, scintigraphic imaging should be performed to evaluate the functional status of the nodule. By scintigraphy, it can be evaluated whether the nodule is hyperactive (hot), normoactive (warm), or hypoactive (cold). Scintigraphic imaging can be performed using radioactive iodine (I-123 or I-131) or 99mTc-pertechnetate. Use of I123 is recommended preferably. Diagnostic testing with I131 is not recommended unless low-uptake thyrotoxicosis is suspected.[1,4]

99mTc-pertechnetat is cheaper, more accessible, and has a shorter shooting time. Although 99mTc-pertechnetate is uptaken, it is not organificated, so it can cause false positive and negative results. Image quality is poor when uptake is low.[4] Although there is no radioactive iodine uptake in 3–8% of the nodules, 99mTc-pertechnetate may be uptaken and cause false positive results. In addition, 99mTc-pertechnetate uptake in the esophagus and vascular structures may also cause false positive imaging.[65]

When there is low thyroid uptake, better imaging can be obtained with I-123 providing better visualization of the retrosternal region, and also true iodine clearance can be measured. However, it is much more expensive and difficult to obtain. The imaging time is generally longer, often using delayed 24th h imaging.[4]

Fine Needle Aspiration Biopsy

FNAB is still the gold standard method for evaluating the thyroid nodules.[14] FNAB is an outpatient method that is easily applied, generally well tolerated, and can be performed with low complication rates. It is a fast and safe method that has high sensitivity, specificity, and precision and also can distinguish between benign and malignant nodules with high accuracy.[18,66]

Cytological evaluation of FNAB

At present, The Bethesda System for Reporting Thyroid Cytopathology (TBSRTC) is the most commonly used classification system for the cytological evaluation of FNAB. TBSRTC is a simplified, 6-category-based reporting system, and its first 2 editions (2010 and 2017) significantly achieved its goal of standardizing thyroid cytopathology reporting. This classification system was updated as the third edition in 2023 in accordance with the terminology of the classification of thyroid neoplasms updated by the World Health Organization in 2022.[66] In this edition, alternative names from the three diagnostic categories that may have caused some confusion in previous editions (the terms "unsatisfactory" for Bethesda 1, "follicular lesion of undetermined significance" for Bethesda 3, "suspicious for follicular neoplasm" for Bethesda 4) have been removed by giving each category a unique name.[67] The RoM rates for adults have been updated for each category based on the results of the prospectively analyzed large series published since 2017.[67]

Although thyroid nodules are less common in childhood than adults, the rate of malignancy for thyroid nodules in children is higher than in adults. It is essential to ensure that the Bethesda system is also used by children.[68] In this edition, ROM rates for childhood thyroid cancers were calculated according to six categories, associated with frequently used practical guidelines, and treatment recommendations are given separately.[67]

Non-diagnostic (Bethesda I): Approximately 15% of FNABs are in the non-diagnostic category.[14] It is difficult to calculate the malignancy risk in this category, since most of the

nodules whose initial FNAB results have been non-diagnostic were not resected. The ROM is 13% in resected nodules whose initial biopsy is reported as non-diagnostic. This rate is higher compared to the entire non-diagnostic cohort.[67]

FNAB should be reperformed in a nodule with an initial biopsy result of non-diagnostic.[14] In nodules with non-diagnostic FNAB results and especially including small cystic components, US-guided second FNAB results in a diagnostic cytology with a rate of 60–80%. Thus, the treatment should be decided according to the recommendations in the relevant category.[67]

If the second FNAB result is Bethesda I again, surgical resection should be considered (Table 3).[69]

Benign (Bethesda 2): Approximately 70% of FNABs result in benign cytology.[14] The ROM is low in nodules with benign cytology. Although it is 4% in resected nodules with benign cytology, the rate is around 1–2% when long-term follow-up nodules are taken into account.[67] US findings of the nodule are important in the follow-up of patients with benign cytology, and this issue is evaluated in the treatment section (Table 3).

Atypia of Undetermined Significance (Bethesta III) Nodules: Bethesda III and IV account for 10–15% of FNAB results.[14] In these nodules, the latest Bethesda classification update recommends FNAB repeat, molecular tests, lobectomy, and clinical follow-up options in adults. The ROM in this category averages 22% in adults according to data based on surgical resection materials. Considering all Bethesda III FNAB results, this rate is likely higher than expected. The mean ROM is slightly higher in children (28%), and repeat FNAB or lobectomy is recommended.[67]

In this category, the ROM differs according to the cytomorphological features considered as atypia. The ROM in nuclear atypia is higher than other atypical features (such as cellular structural atypia, oncocytic atypia, and lymphocytic atypia).[70,71]

In the latest update of the Bethesda classification, it has been suggested that the Bethesda III category be divided into two subclasses: Nuclear and other atypia. In particular, the presence of nuclear atypia is important for the cytopathologist to warn the clinician that the ROM is higher.[67] Making this distinction can make a significant contribution to the selection for the application of molecular tests, especially in the nuclear atypia group.[71]

In this category, the decision should be made according to the patient's clinical risk factors, US characteristics of the nodule, available facilities, and the patient's preference. FNAB is repeated considering the factors related to the patient and the nodule. If FNAB result is still in the undetermined group or there are nodules with high risk factors, diagnostic lobectomy should be performed. Nodules with low-risk features can be followed by US.[14] After the patient is informed regarding the characteristics of the nodule and treatment options, diagnostic lobectomy can be considered in case the patient is unwilling to be followed up (Table 3).

Follicular Neoplasm (Bethesda IV): The ROM is 30% in adults and 50% in children in this category. Molecular tests can be used for risk assessment in adults.[72]

Surgical resection is recommended in children since the malignancy rate is higher. Surgical resection, often hemithyroidectomy or lobectomy, is recommended for the treatment of nodules diagnosed with follicular neoplasia (Table 3).[67]

Table 3. The 2023 Bethesda System for Reporting Thyroid Cytopathology (This table is established using The 2023 Bethesda System for Reporting Thyroid Cytopathology guideline (67))

		Adult		Pediatric	
Diagnostic Category		ROM %Mean (min-max)	Usual Management	ROM %Mean (min-max)	Usual Management
Nondiagnostic	Bethesda I	%13 (5-20)	Repeat FNA with ultrasound guidance	%14 (0-33)	Repeat FNA with ultrasound guidance
Benign	Bethesda II	%4 (2-7)	Clinical and ultrasound follow-up	%6 (0-27)	Clinical and ultrasound follow-up
Atypia of undetermined significance	Bethesda III	%22 (13-30)	Repeat FNA, molecular testing, lobectomy, surveillance	%28 (11-54)	Repeat FNA, lobectomy
Follicular Neoplasm	Bethesda IV	%30 (23-34)	Molecular testing, diagnostic lobectomy	%50 (%58-100)	Surgical resection
Suspicious for malignancy	Bethesda V	%74 (67-83)	Molecular testing, lobectomy or near-total thyroidectomy	%81 (40-100)	Surgical resection
Malignant	Bethesda VI	%97 (97-100)	Lobectomy or near-total thyroidectomy	%98 (86-100)	Surgical resection

Suspicious for Malignancy (Bethesda V): In this category, the ROM is reported as 74%. Molecular tests can be used to determine the extent of surgery.[67]

In these patients, lobectomy or total or near-total thyroidectomy can be performed (Table 3).[67]

Malignant (Bethesda VI): This category includes malignant results of different tumor types diagnosed according to the cytomorphological features in FNAB. The average ROM is 97%. The type of surgery should be determined according to the type and characteristics of the tumor. In metastatic tumors, necessary investigations should be made about the primary tumor. Depending on the type of primary tumor, there may not be an indication for surgery of the thyroid (Table 3).[67]

Number of nodules to be biopsied

FNAB may be indicated for more than one nodule according to US features of the thyroid. Biopsy of three or more nodules is not well tolerated by patients. Cost increases without significant a benefit, and there are some additional risks. If FNAB is indicated in three or more nodules considering the ACR TI-RADS classification, it is recommended to biopsy two of the most suspicious nodules according to their total scores.[26]

Immunohistochemical studies in FNAB

Immunohistochemical method is a good method for detecting malignancy in paraffin block tissue. CD56 negativity, CK19, HBME-1, and galectin-3 positivity are some of the most appropriate markers in the differential diagnosis of malignant and benign lesions of the thyroid.[68] Although the use of these immunohistochemical markers in FNAB specimens has been limited to date, some studies have reported that a single or a combination of two or three may contribute to the detection of malignancy in FNAB specimens. In the latest meta-analysis, Galectin-3, HBME-1, CK-19, CD-56, and TPO are stated as high-confidence marker candidates whose efficacy should be confirmed in thyroid cytology.[73]

Although immunohistochemical analysis of FNAB smears increases the overall diagnostic accuracy, more studies are needed to determine the best immune panel.

Molecular tests in FNAB

There have been rapid developments in the past 15–20 years in cytomolecular tests, which are used to reduce the need for diagnostic surgery, especially in FNAB samples diagnosed with Bethesda III and IV.[74]

The three molecular tests most commonly used in the United States today, each using different methods, are Afirma Genomic Sequencing Classifier (Afirma GSC), ThyGeNEXT/ThyraMIR (MPTX) and Thyroseqv3 (TSv3). Molecular tests can be classified as "rule in" and "rule out" based on their ability to confirm or exclude malignancy.[74]

Vargas-Salas et al. [75] reported that a robust "rule out" test with a thyroid cancer prevalence value of 20–40% requires a minimum negative predictive value of 94% and a minimum sensitivity of 90%; however, they found that a "rule in" test for malignancy required a positive predictive value of at least 60% and a specificity >80%. MPTX, Afirma GSC, and TSv3 all demonstrated to perform well as undiagnosed (Bethesda III and IV) "exclusion" tests based on their relatively high sensitivity and negative predictive values. However, their diagnostic confirmatory performance for malignancy is still limited (Table 3).[74]

Molecular testing for thyroid nodules and thyroid cancer increases the diagnostic accuracy of indeterminate thyroid nodules. Although the use of molecular tests is increasing, the cost of molecular tests varies between 3000 and 5000 dollars and the most important problem is still the cost of testing.

Tru-cut biopsy

FNAB is the first-line diagnostic tool in thyroid nodules, and there is no difference in diagnostic performance between FNAB and thick needle biopsy.[76] Although FNAB is sufficient for the evaluation of many nodules, tru-cut biopsy (with 18–21 gauge needle) is recommended in some rare cases. In recent years, the use of tru-cut biopsy has been increasing as an alternative, especially in non-diagnostic (Bethesta I, III, and IV) biopsied thyroid nodules.[68] Tru-cut biopsy has low non-diagnostic outcome rates and high specificity for the diagnosis of malignancy in thyroid nodules whose initial FNAB is non-diagnostic. Tru-cut biopsy is indicated as a safe diagnostic technique with higher diagnostic efficiency and low complication rate, especially in cases where molecular testing is not available or FNAB cannot obtain enough cells for molecular testing.[77]

Tru-cut biopsy may be considered in second biopsies, especially in selected patients for whom it is difficult to obtain sufficient samples in FNAB. In addition, in fast-growing thyroid masses with suspected ATC or thyroid lymphoma, it is more appropriate to prefer tru-cut biopsy instead of FNAB as the first diagnostic tool.

Treatment and Follow-up

Follow-up in Benign (Bethesta II) Nodules: There is no consensus in the guidelines regarding the follow-up period. According to the guidelines of the American Association of Endocrinologists, nodules with benign cytological findings and no clinical and US risk factors can be followed up if they are asymptomatic.

The follow-up of nodules with benign FNAB is defined in the ATA guideline and these follow-up criteria are written in next sections. Since the false negative rate in FNAB is low, it is common practice to follow up most of the nodules with benign FNAB results with US. Since US nodule features rather than enlargement are associated with high missed malignancy, it is recommended to follow-up thyroid nodules with benign cytology according to the risk classification in US.[1,4,46]

US control and repeat FNAB within 6–12 months are recommended for nodules with highly suspected US features and benign FNAB results. If they are benign in the second FNAB, these nodules can be followed by US.[1,4] US should be repeated within 12–24 months in nodules with low and moderate suspicious US features. If there is enlargement on US (20% increase in at least two nodule dimensions with a minimal increase of 2 mm or more than a 50% change in volume) or new suspicious US features develop, FNAB should be repeated or follow-up with repeated USs should be continued. If growth continues in US follow-up, FNAB should be repeated.[1]

The use of US in the follow-up of very low suspicious nodules (including spongioform nodules) and the evaluation of nodule enlargement as an indicator in repeat biopsy are limited in detecting missed malignancy. If US is to be repeated, it should be performed after 24 months.[1]

If the repeated US-guided FNAB of the nodule is benign, then US follow-up is not required for the continuation of the malignancy risk.[1] To exclude this nodule from follow-up, it is important that it is asymptomatic and has no suspicious US features.[4] This method can be applied for solitary nodules. However, in MNG, long-term follow-up is usually required.[18]

The follow-up of nodules that do not meet the FNAB criteria in the initial evaluation is going to be decided according to the recommendations of the ATA guideline and ACR TI-RADS guideline.[1,26] It is recommended to repeat US in 6–12 months for nodules <1 cm with highly suspicious USG features, and annual US control for 5 years for nodules >×0.5 cm in ACR TI-RADS 5 is recommended.[1,26]

For nodules of <1 cm with moderate suspicious US features, ATA recommends follow-up with US at 12–24-month intervals. American Radiology Association recommends follow-up with US in TIRADS 4 >1 cm nodules at 1st, 2nd, 3rd, and 5th years.

In nodules with low suspicious US features, ATA recommends follow-up with US at 12–24-month intervals, and very low-risk nodules at intervals longer than 24 months and in TIRADS 3 for >1.5 cm nodules at 1st, 3rd, and 5th years. Follow-up is not recommended for benign (TIRADS 1) and not suspicious nodules (TIRADS 2).[1,26] If the ACR TI-RADS score increases in follow-up nodules compared to the previous control, a repeat US control should be performed 1 year later, regardless of the initial TIRADS score. The American Radiology Association guideline stated that the absence of any change in the size of a nodule under follow up period of 5-years can safely indicate that the nodule is benign, and US follow-up of these nodules can be terminated.[26]

FNAB should be repeated in nodules with a 20% (2 mm and above) increase in at least 2 diameters of the nodule or more than 50% increase in the nodule volume or in case new suspicious US features are detected in the follow-up.[1]

Routine US follow-up is not required in very low-risk nodules and cysts smaller than 1 cm due to the ATA guideline. However, in very low-risk nodules or cysts larger than 1 cm, US follow-up and time interval are unknown. If follow-up is to be carried out, US should be repeated at intervals longer than at least 24 months.[1]

Medical Treatment

L-thyroxine suppression therapy is not recommended for benign nodules. L-thyroxine therapy is not recommended to prevent recurrence in individuals with normal serum TSH levels after lobectomy. Appropriate iodine intake should be provided in young patients with a follow-up nodule, iodine support can be given in followed-up patients who are not thought to have adequate iodine intake. L-thyroxine replacement therapy is recommended in young patients with subclinical hypothyroidism due to autoimmune thyroiditis.[4]

Surgical Treatment

Surgical treatment may be required for nodules that cause symptoms such as breathing and swallowing difficulties due to compression on the trachea and esophagus or for cosmetic reasons.[11,19,78]

Progressive nodule enlargement can be an indication for thyroidectomy.[1] Although there is no exact nodule diameter established for the surgery, some researchers recommend thyroidectomy for Bethesda II-diagnosed nodules larger than 3 or 4 cm because of the higher false-negative FNAB rate and higher RoM.[79-81]

However, in some other studies, it has been reported that the malignancy rates are not higher in nodules larger than 4 cm compared to nodules smaller than 4 cm, and nodules larger than 4 cm should be individualized according to clinical, ultrasonographic, and cytological characteristics rather than routine surgical resection based on size alone.[82,83]

While making a decision in these patients, it would be ap-

propriate to share the nodule characteristics and different recommendations with the patient, and to choose the treatment method specifically with the patient. In undetermined categories (Bethesda I, III, and IV) diagnostic lobectomy can be performed.[67]

Although there are benign FNAB findings, surgery can be considered in nodules with suspicious US features for malignancy. Thyroidectomy may be required in hyperfunctional nodules (solitary nodule or toxic MNG).[11]

When surgery is needed, the extent of the resection (lobectomy or total or near-total thyroidectomy) depends on many factors such as diagnosis of disease, symptoms, presence of nodules in the contralateral lobe, functional status of the thyroid, comorbidities, family history, surgical risk, and patient preference.[11]

Radioactive Iodine Therapy

In toxic multinodular or nodular goiter; radioactive iodine treatment may be preferred in elderly patients, patients with significant comorbidities, and patients who have undergone thyroid surgery before. In addition, if there is an indication for FNAB in the accompanying cold nodule according to the US features, FNAB should be performed from this nodule.[84]

Non-Surgical Interventional Procedures

Non-surgical interventional procedures are increasing, especially in symptomatic solid benign thyroid nodules, thyroid cysts, and toxic nodules. These methods include ultrasound-guided ablation procedures, percutaneous ethanol injection, or ultrasound-guided ablation procedures involving the application of heat in the form of laser, radiofrequency, high-intensity focused US, or microwave energy. Thermal ablation can be used in solid and growing nodules, but the benign nature of the lesion should be confirmed with 2 FNABs and calcitonin should be measured. In low-risk ultrasound features or in autonomous nodules, a single FNAB with benign cytology is sufficient.[11] Radiofrequency ablation is more commonly used in symptomatic solid nodules and toxic nodules. It can reduce the nodule volume by approximately 75%. Repeated ablations may increase the response rate.

Completely cystic or predominantly cystic (>80% cyst) nodules that recur after initial aspiration and cause compression symptoms are ideal candidates for percutaneous ethanol injection. With volume reduction, more than 80% of patients permanently improve their compression symptoms.

These procedures should not be performed in patients who are asymptomatic and do not have significant esthetic complaints.[85]

Since the morphological features of nodules treated with ablative methods may change over time, they should be followed clinically and ultrasonographically. If regrowth occurs at follow-up, evaluation with a new FNAB is required to continue follow-up or before re-ablation. Appropriate patient selection and an experienced practitioner are the main factors that increase the success rate while minimizing the risk of complications for all these ablative procedures.[11,85]

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References

1. Haugen BR, Alexander EK, Bible KC, Doherty GM, Mandel SJ, Nikiforov YE, et al. 2015 American Thyroid Association Management guidelines for adult patients with thyroid nodules and differentiated thyroid cancer: the American Thyroid Association Guidelines Task Force on Thyroid Nodules and Differentiated Thyroid Cancer. Thyroid 2016 ;26:1-133. [CrossRef]
2. Seib CD, Sosa JA. Evolving understanding of the epidemiology of thyroid cancer. Endocrinol Metab Clin North Am 2019;48:23-35. [CrossRef]
3. Detweiler K, Elfenbein DM, Mayers D. Evaluation of thyroid nodules. Surg Clin North Am 2019;99:571-86. [CrossRef]
4. Gharib H, Papini E, Garber JR, Duick DS, Harrell RM, Hegedüs L, et al. American Association of Clinical Endocrinologists, American College of Endocrinology, and Associazione Medici Endocrinologi medical guidelines for clinical practice for the diagnosis and management of thyroid nodules--2016 update. Endocr Pract 2016;22:622-39. [CrossRef]
5. Hegedüs L, Bonnema SJ, Bennedbaek FN. Management of simple nodular goiter: current status and future perspectives. Endocr Rev 2003;24:102-32. [CrossRef]
6. Lee J, Delbridge L. Tiroid Nodüllerine Yaklaşım. In: İşgör A, Uludağ M, editors. Tiroit. 1st ed. İstanbul: Nobel Tıp Kitabevleri; 2013. p. 249-63.
7. Knobel M. Etiopathology, clinical features, and treatment of diffuse and multinodular nontoxic goiters. J Endocrinol Invest 2016;39:357-73. [CrossRef]
8. Baloch ZW, Asa SL, Barletta JA, Ghossein RA, Juhlin CC, Jung CK, et al. Overview of the 2022 WHO classification of thyroid neoplasms. Endocr Pathol 2022;33:27-63. [CrossRef]
9. Kamani T, Charkhchi P, Zahedi A, Akbari MR. Genetic susceptibility to hereditary non-medullary thyroid cancer. Hered Cancer Clin Pract 2022;20:9. [CrossRef]

10. Wells SA Jr, Asa SL, Dralle H, Elisei R, Evans DB, Gagel RF, et al. Revised American Thyroid Association guidelines for the management of medullary thyroid carcinoma. Thyroid 2015;25:567-610. [CrossRef]
11. Grani G, Sponziello M, Pecce V, Ramundo V, Durante C. Contemporary thyroid nodule evaluation and management. J Clin Endocrinol Metab 2020;105:2869-83. [CrossRef]
12. Jasim S, Baranski TJ, Teefey SA, Middleton WD. Investigating the effect of thyroid nodule location on the risk of thyroid cancer. Thyroid 2020;30:401-7. [CrossRef]
13. Burgos N, Ospina NS, Sipos JA. The future of thyroid nodule risk stratification. Endocrinol Metab Clin North Am 2022;51:305-21. [CrossRef]
14. Tamhane S, Gharib H. Thyroid nodule update on diagnosis and management. Clin Diabetes Endocrinol 2016;2:17. [CrossRef]
15. Kobaly K, Kim CS, Mandel SJ. Contemporary management of thyroid nodules. Annu Rev Med 2022;73:517-28. [CrossRef]
16. Holt EH. Current evaluation of thyroid nodules. Med Clin North Am 2021;105:1017-31. [CrossRef]
17. Sharbidre KG, Lockhart ME, Tessler FN. Incidental thyroid nodules on ımaging: relevance and management. Radiol Clin North Am 2021;59:525-33. [CrossRef]
18. Maxwell C, Sipos JA. Clinical diagnostic evaluation of thyroid nodules. Endocrinol Metab Clin North Am 2019;48:61-84. [CrossRef]
19. Patel KN, Yip L, Lubitz CC, Grubbs EG, Miller BS, Shen W, et al. The American Association of Endocrine Surgeons guidelines for the definitive surgical management of thyroid disease in adults. Ann Surg 2020;271:e21-93. [CrossRef]
20. Unlu MT, Kostek M, Aygun N, Isgor A, Uludag M. Non-toxic multinodular goiter: from etiopathogenesis to treatment. Sisli Etfal Hastan Tip Bul 2022;56:21-40. [CrossRef]
21. Durante C, Costante G, Lucisano G, Bruno R, Meringolo D, Paciaroni A, et al. The natural history of benign thyroid nodules. JAMA 2015;313:926-35. [CrossRef]
22. Negro R. What happens in a 5-year follow-up of benign thyroid nodules. J Thyroid Res 2014;2014:459791. [CrossRef]
23. Gharib H, Papini E. Thyroid nodules: clinical importance, assessment, and treatment. Endocrinol Metab Clin North Am 2007;36:707-35. [CrossRef]
24. Hegedüs L. Clinical practice. The thyroid nodule. N Engl J Med 2004;351:1764-71. [CrossRef]
25. Jarløv AE, Nygaard B, Hegedüs L, Hartling SG, Hansen JM. Observer variation in the clinical and laboratory evaluation of patients with thyroid dysfunction and goiter. Thyroid 1998;8:393-8. [CrossRef]
26. Tessler FN, Middleton WD, Grant EG, Hoang JK, Berland LL, Teefey SA, et al. ACR Thyroid Imaging, Reporting and Data System (TI-RADS): white paper of the ACR TI-RADS committee. J Am Coll Radiol 2017;14:587-95. [CrossRef]
27. Isgor A, Uludag M, Aygun N, (editors). Handbook of Thyroid Parathyroid Adrenal. 1st ed. Istanbul: BAU Publications; 2023. p.27-31.
28. Isgor A, Uludag M, Aygun N, (editors). Handbook of Thyroid Parathyroid Adrenal. 1st ed. Istanbul: BAU Publications; 2023. p. 19-26.
29. Baloch Z, Carayon P, Conte-Devolx B, Demers LM, Feldt-Rasmussen U, Henry JF, et al; Guidelines Committee, National Academy of Clinical Biochemistry. Laboratory medicine practice guidelines. Laboratory support for the diagnosis and monitoring of thyroid disease. Thyroid 2003;13:3-126. [CrossRef]
30. Petric R, Besic H, Besic N. Preoperative serum thyroglobulin concentration as a predictive factor of malignancy in small follicular and Hürthle cell neoplasms of the thyroid gland. World J Surg Oncol 2014;12:282. [CrossRef]
31. Hulikal N, Re A, Banoth M, Chowhan AK, Yutla M, Sachan A. Can preoperative serum thyroglobulin levels predict the risk of malignancy? Results from prospective analysis of biochemical predictors of malignancy in thyroid nodules. Acta Otorhinolaryngol Ital 2020;40:33-7. [CrossRef]
32. Yazici P, Mihmanli M, Bozkurt E, Ozturk FY, Uludag M. Which is the best predictor of thyroid cancer: thyrotropin, thyroglobulin or their ratio? Hormones (Athens) 2016;15:256-63. [CrossRef]
33. Elisei R, Bottici V, Luchetti F, Di Coscio G, Romei C, Grasso L, et al. Impact of routine measurement of serum calcitonin on the diagnosis and outcome of medullary thyroid cancer: experience in 10,864 patients with nodular thyroid disorders. J Clin Endocrinol Metab 2004;89:163-8. [CrossRef]
34. Broecker-Preuss M, Simon D, Fries M, Kornely E, Weber M, Vardarli I, et al. Update on calcitonin screening for medullary thyroid carcinoma and the results of a retrospective analysis of 12,984 patients with thyroid nodules. Cancers (Basel) 2023;15:2333. [CrossRef]
35. Verbeek HH, de Groot JWB, Sluiter WJ, Muller Kobold AC, van den Heuvel ER, Plukker JT, et al. Calcitonin testing for detection of MTC in people with thyroid nodules. Cochrane Database Syst Rev 2020;3:CD010159. [CrossRef]
36. Smith-Bindman R, Lebda P, Feldstein VA, Sellami D, Goldstein RB, Brasic N, et al. Risk of thyroid cancer based on thyroid ultrasound imaging characteristics: results of a population-based study. JAMA Intern Med 2013;173:1788-96. [CrossRef]
37. Brito JP, Gionfriddo MR, Al Nofal A, Boehmer KR, Leppin AL, Reading C, et al. The accuracy of thyroid nodule ultrasound to predict thyroid cancer: systematic review and meta-analysis. J Clin Endocrinol Metab 2014;99:1253-63. [CrossRef]
38. Langer JE, Agarwal R, Zhuang H, Huang SS, Mandel SJ. Correlation of findings from iodine 123 scan and ultrasonography in the recommendation for thyroid fine-needle aspiration biopsy. Endocr Pract 2011;17:699-706. [CrossRef]
39. Lau LW, Ghaznavi S, Frolkis AD, Stephenson A, Robertson HL, Rabi DM, et al. Malignancy risk of hyperfunctioning thyroid nodules compared with non-toxic nodules: systematic review and a meta-analysis. Thyroid Res 2021;14:3. [CrossRef]

40. Rosario PW, de Castro Nicolau T. The value of ultrasonography for the indication of fine-needle aspiration in autonomous thyroid nodules. Diagn Cytopathol 2021;49:363-6. [CrossRef]
41. Pereira-Macedo J, Freire B, Macedo-Oliveira C, Mendes J, Carvalho M, Rocha-Neves J, et al. Hyperfunctioning papillary thyroid carcinoma - a case report and literature review. Acta Chir Belg 2023;9:1-6. [CrossRef]
42. Mirfakhraee S, Mathews D, Peng L, Woodruff S, Zigman JM. A solitary hyperfunctioning thyroid nodule harboring thyroid carcinoma: review of the literature. Thyroid Res 2013;6:7. [CrossRef]
43. Goonoo MS, Arshad MF, Tahir F, Balasubramanian SP. Toxic adenoma: to biopsy or not to biopsy? Ann R Coll Surg Engl 2021;103:e319-23. [CrossRef]
44. Kim EK, Park CS, Chung WY, Oh KK, Kim DI, Lee JT, et al. New sonographic criteria for recommending fine-needle aspiration biopsy of nonpalpable solid nodules of the thyroid. AJR Am J Roentgenol 2002;178:687-91. [CrossRef]
45. Frates MC, Benson CB, Charboneau JW, Cibas ES, Clark OH, Coleman BG, et al. Management of thyroid nodules detected at US: Society of Radiologists in Ultrasound consensus conference statement. Radiology 2005;237:794-800. [CrossRef]
46. Shin JH, Baek JH, Chung J, Ha EJ, Kim JH, Lee YH, et al. Ultrasonography diagnosis and ımaging-based management of thyroid nodules: revised Korean Society of Thyroid Radiology consensus statement and recommendations. Korean J Radiol 2016;17:370-95. [CrossRef]
47. Horvath E, Majlis S, Rossi R, Franco C, Niedmann JP, Castro A, et al. An ultrasonogram reporting system for thyroid nodules stratifying cancer risk for clinical management. J Clin Endocrinol Metab 2009;94:1748-51. [CrossRef]
48. Park JY, Lee HJ, Jang HW, Kim HK, Yi JH, Lee W, et al. A proposal for a thyroid imaging reporting and data system for ultrasound features of thyroid carcinoma. Thyroid 2009;19:1257-64. [CrossRef]
49. Kwon D, Kulich M, Mack WJ, Monedero RM, Joyo E, Angell TE. Malignancy risk of thyroid nodules that are not classifiable by the American Thyroid Association Ultrasound Risk Stratification System: a systematic review and meta-analysis. Thyroid 2023;33:593-602. [CrossRef]
50. Papini E, Guglielmi R, Bianchini A, Crescenzi A, Taccogna S, Nardi F, et al. Risk of malignancy in nonpalpable thyroid nodules: predictive value of ultrasound and color-Doppler features. J Clin Endocrinol Metab 2002;87:1941-6. [CrossRef]
51. Moon HJ, Kwak JY, Kim MJ, Son EJ, Kim EK. Can vascularity at power Doppler US help predict thyroid malignancy? Radiology 2010;255:260-9. [CrossRef]
52. Yang GCH, Fried KO. Most thyroid cancers detected by sonography lack intranodular vascularity on color Doppler imaging: review of the literature and sonographic-pathologic correlations for 698 thyroid neoplasms. J Ultrasound Med 2017;36:89-94. [CrossRef]
53. Khadra H, Bakeer M, Hauch A, Hu T, Kandil E. Is vascular flow a predictor of malignant thyroid nodules? A meta-analysis. Gland Surg 2016;5:576-82. [CrossRef]
54. Lai X, Liu M, Xia Y, Wang L, Bi Y, Li X, et al. Hypervascularity is more frequent in medullary thyroid carcinoma: compared with papillary thyroid carcinoma. Medicine (Baltimore) 2016;95:e5502. [CrossRef]
55. Jiang L, Zhang D, Chen YN, Yu XJ, Pan MF, Lian L. The value of conventional ultrasound combined with superb microvascular imaging and color Doppler flow imaging in the diagnosis of thyroid malignant nodules: a systematic review and meta-analysis. Front Endocrinol (Lausanne) 2023;14:1182259. [CrossRef]
56. Sidhu PS, Cantisani V, Dietrich CF, Gilja OH, Saftoiu A, Bartels E, et al. The EFSUMB guidelines and recommendations for the clinical practice of Contrast-Enhanced Ultrasound (CEUS) in nonhepatic applications: update 2017 (long version). Ultraschall Med 2018;39:e2-44. [CrossRef]
57. Wu Y, Zhou C, Shi B, Zeng Z, Wu X, Liu J. Systematic review and meta-analysis: diagnostic value of different ultrasound for benign and malignant thyroid nodules. Gland Surg 2022;11:1067-77. [CrossRef]
58. Yu Y, Shi LL, Zhang HW, Wang Q. Performance of contrast-enhanced ultrasound for lymph node metastasis in papillary thyroid carcinoma: a meta-analysis. Endocr Connect 2023;12:e220341. [CrossRef]
59. Radzina M, Ratniece M, Putrins DS, Saule L, Cantisani V. Performance of Contrast-Enhanced Ultrasound in thyroid nodules: review of current state and future perspectives. Cancers (Basel) 2021;13:5469. [CrossRef]
60. Shiina T, Nightingale KR, Palmeri ML, Hall TJ, Bamber JC, Barr RG, et al. WFUMB guidelines and recommendations for clinical use of ultrasound elastography: part 1: basic principles and terminology. Ultrasound Med Biol 2015;41:1126-47. [CrossRef]
61. Azizi G, Keller J, Lewis M, Puett D, Rivenbark K, Malchoff C. Performance of elastography for the evalu ation of thyroid nodules: a prospective study. Thyroid 2013;23:734-40. [CrossRef]
62. Zhang D, Wang XN, Jiang L, Yu CX, Chen YN, Yu XJ, et al. Conventional ultrasonography and elastosonography in diagnosis of malignant thyroid nodules: a systematic review and meta-analysis. Front Endocrinol (Lausanne) 2023;13:1082881. [CrossRef]
63. Lei R, Wang Z, Qian L. Ultrasonic characteristics of medullary thyroid carcinoma: differential from papillary thyroid carcinoma and benign thyroid nodule. Ultrasound Q 2021;37:329-35. [CrossRef]
64. Liu MJ, Liu ZF, Hou YY, Men YM, Zhang YX, Gao LY, et al. Ultrasonographic characteristics of medullary thyroid carcinoma: a comparison with papillary thyroid carcinoma. Oncotarget 2017;8:27520-8. [CrossRef]
65. Bahn RS, Castro MR. Approach to the patient with nontoxic multinodular goiter. J Clin Endocrinol Metab 2011;96:1202-12. [CrossRef]
66. Rossi ED, Baloch Z. The impact of the 2022 WHO classification of thyroid neoplasms on everyday practice of cytopathology. Endocr Pathol 2023;34:23-33. [CrossRef]
67. Ali SZ, Baloch ZW, Cochand-Priollet B, Schmitt FC, Vielh P, VanderLaan PA. The 2023 Bethesda system for reporting thyroid cytopathology. Thyroid 2023 Jul 8. doi: 10.1089/thy.2023.0141. [Epub ahead of print]. [CrossRef]

68. Antonia TD, Maria LI, Ancuta-Augustina GG. Preoperative evaluation of thyroid nodules - Diagnosis and management strategies. Pathol Res Pract 2023;246:154516. [CrossRef]
69. Cibas ES, Ali SZ. The 2017 Bethesda system for reporting thyroid cytopathology. Thyroid 2017;27:1341-46. [CrossRef]
70. Cherella CE, Hollowell ML, Smith JR, Zendejas B, Modi BP, Cibas ES, et al. Subtype of atypia on cytology and risk of malignancy in pediatric thyroid nodules. Cancer Cytopathol 2022;130:330-5. [CrossRef]
71. Glass RE, Levy JJ, Motanagh SA, Vaickus LJ, Liu X. Atypia of undetermined significance in thyroid cytology: nuclear atypia and architectural atypia are associated with different molecular alterations and risks of malignancy. Cancer Cytopathol 2021;129:966-72. [CrossRef]
72. Carty SE, Ohori NP, Hilko DA, McCoy KL, French EK, Manroa P, et al. The clinical utility of molecular testing in the management of thyroid follicular neoplasms (Bethesda IV nodules). Ann Surg 2020;272:621-7. [CrossRef]
73. Mohan U, Sunny SP, Mendonca P, Kuriakose MA, Kannan S, Suresh A. Systematic review and meta-analysis to ıdentify the ımmunocytochemical markers effective in delineating benign from malignant thyroid lesions in FNAC samples. Endocr Pathol 2022;33:243-56. [CrossRef]
74. Patel J, Klopper J, Cottrill EE. Molecular diagnostics in the evaluation of thyroid nodules: current use and prospective opportunities. Front Endocrinol (Lausanne) 2023;14:1101410. [CrossRef]
75. Vargas-Salas S, Martínez JR, Urra S, Domínguez JM, Mena N, Uslar T, et al. Genetic testing for indeterminate thyroid cytology: review and meta-analysis. Endocr Relat Cancer 2018;25:R163-77. [CrossRef]
76. Cao H, Kao RH, Hsieh MC. Comparison of core-needle biopsy and fine-needle aspiration in screening for thyroid malignancy: a systematic review and meta-analysis. Curr Med Res Opin 2016;32:1291-301. [CrossRef]
77. Suh CH, Baek JH, Park C, Choi YJ, Lee JH. The role of core needle biopsy for thyroid nodules with initially indeterminate results on previous fine-needle aspiration: a systematic review and meta-analysis. AJNR Am J Neuroradiol 2017;38:1421-6. [CrossRef]
78. Bernet VJ, Chindris AM. Update on the evaluation of thyroid nodules. J Nucl Med 2021;62:13S-9. [CrossRef]
79. Bakkar S, Poma AM, Corsini C, Miccoli M, Ambrosini CE, Miccoli P. Underestimated risk of cancer in solitary thyroid nodules ≥3 cm reported as benign. Langenbecks Arch Surg 2017;402:1089-94. [CrossRef]
80. Wharry LI, McCoy KL, Stang MT, Armstrong MJ, LeBeau SO, Tublin ME, et al. Thyroid nodules (≥4 cm): can ultrasound and cytology reliably exclude cancer? World J Surg 2014;38:614-21. [CrossRef]
81. Giles WH, Maclellan RA, Gawande AA, Ruan DT, Alexander EK, Moore FD Jr, et al. False negative cytology in large thyroid nodules. Ann Surg Oncol 2015;22:152-7. [CrossRef]
82. Tang JZ, Chua JME, Woon TK, Tan BS, Kiong KL. Large thyroid nodules: should size alone matter? Eur Arch Otorhinolaryngol 2022;279:3139-46. [CrossRef]
83. Kizilgul M, Shrestha R, Radulescu A, Evasovich MR, Burmeister LA. Thyroid nodules over 4 cm do not have higher malignancy or benign cytology false-negative rates. Endocrine 2019;66:249-53. [CrossRef]
84. Ross DS, Burch HB, Cooper DS, Greenlee MC, Lauberg P, Mala AL, et al. 2016 American Thyroid Association guidelines for diagnosis and management of hyperthyroidism and other causes of thyrotoxicosis. Thyroid 2016;26:1343-421. [CrossRef]
85. Stan MN, Papaleontiou M, Schmitz JJ, Castro MR. Nonsurgical management of thyroid nodules: the role of ablative therapies. J Clin Endocrinol Metab 2022;19;107:1417-30. [CrossRef]