Review article

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THYROID NODULES: NAVIGATING THE DIAGNOSTIC PATHWAY

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Thyroid nodules (TNs) are a common clinical finding, and the main diagnostic challenge lies in differentiating benign from malignant lesions. Clinical and laboratory evaluation forms the foundation of the initial work-up, whereas ultrasound-based risk stratification systems guide the decision on fine-needle aspiration biopsy (FNAB). The Bethesda system remains the gold standard for cytological diagnosis, with its latest edition providing clearer diagnostic categories and management recommendations. Nevertheless, nearly one-third of cases remain indeterminate, frequently leading to diagnostic surgery. In such instances, molecular testing enables more precise risk stratification through rule-out and rule-in approaches, while functional imaging modalities, such as [^99mTc]Tc-MIBI scintigraphy and [^18F]FDG PET/CT, further contribute to reducing unnecessary surgical interventions. Emerging ultrasound techniques, including superb microvascular imaging (SMI), contrast-enhanced ultrasound

(CEUS), and elastography, demonstrate promising potential, although their routine clinical application has yet to be standardized. Artificial intelligence in ultrasound diagnostics, cytology, and radiomics offers new perspectives, but its clinical utility still requires confirmation in large prospective studies.

Keywords: thyroid lesions, differential diagnosis, ultrasound, FNAB, molecular testing, artificial intelligence.

Pregledni rad

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TIROIDNI NODUSI: DIJAGNOSTIČKI PUTOKAZI

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Tiroidni nodusi (TN) predstavljaju čest klinički nalaz, a glavni dijagnostički izazov je diferenciranje benignih od malignih lezija. Klinička i laboratorijska evaluacija čine osnovu inicijalnog pristupa, dok ultrazvučni sistemi procene rizika usmeravaju odluku o aspiracionoj biopsiji (engl. fine-needle aspiration biopsy, FNAB). Bethesda sistem ostaje zlatni standard citološke dijagnostike, a novo izdanje donelo je jasnije definisane dijagnostičke kategorije i preporuke za dalje lečenje. Ipak, gotovo trećina nalaza ostaje indeterminisana, što često vodi ka dijagnostičkoj hirurgiji. U takvim slučajevima, molekularni testovi omogućavaju precizniju procenu rizika, dok funkcionalne imidžing metode, poput [^99mTc]Tc-MIBI scintigrafije i [^18F]FDG PET/CT-a, dodatno doprinose smanjenju broja nepotrebnih operacija. Novije ultrazvučne tehnike, uključujući superb mikrovaskularno snimanje (engl. superb microvascular imaging, SMI), kontrastno pojačan ultrazvuk (engl. contrast-enhanced ultrasound, CEUS) i elastografiju, pokazuju potencijal, iako njihova rutinska primena još nije standardizovana. Primena veštačke inteligencije u ultrazvučnoj dijagnostici, citologiji i radiomici otvara nove

perspektive, ali njena klinička vrednost tek treba da bude potvrđena u velikim prospektivnim studijama.

Ključne reči: tiroidne lezije, diferencijalna dijagnoza, ultrazvuk, FNAB, molekularno testiranje, veštačka inteligencija.

INTRODUCTION

Thyroid nodules (TNs) are a common finding in the general population, with prevalence rates varying considerably by diagnostic method. Due to the widespread use of ultrasound (US) and other high-resolution imaging modalities, detection rates have markedly increased in recent decades (1). While palpation detects TNs in approximately 3% of adults, US-based studies suggest that their prevalence may reach up to 60% (2).

Despite this high detection rate, the majority of TNs are benign, whereas malignancy is confirmed in approximately 7–15% of cases, most commonly as papillary thyroid carcinoma (PTC) (1,3). Importantly, the rising incidence has not been accompanied by a parallel increase in mortality, underscoring the growing detection of biologically indolent, subclinical forms of disease (4,5). In this context, rational selection of patients for further diagnostic work-up and treatment remains a key issue in contemporary endocrinology.

For optimal clinical decision-making, the current diagnostic approach to TNs relies on a multimodal evaluation that integrates clinical assessment, laboratory testing, scintigraphy, US, and, when indicated, cytological analysis and molecular diagnostics. In recent years, artificial intelligence (AI)–based tools have also emerged as promising aids for risk stratification.

This review aims to provide an overview of current guidelines and contemporary methods of risk assessment, with particular emphasis on differentiating benign from malignant thyroid nodules, and to highlight the most recent evidence from the literature.

CLINICAL EVALUATION

TNs, whether detected during clinical examination or incidentally through imaging performed for unrelated reasons, should be evaluated with regard to malignant potential, thyroid functional status (hypo- or hyperthyroidism), and the presence of compressive symptoms or signs.

History

Historical features associated with an increased risk of malignancy include (6–8): (I) rapid enlargement of the nodule; (II) history of head and neck irradiation during childhood (particularly therapeutic exposure, including total-body irradiation prior to hematopoietic stem cell transplantation); (III) family history of thyroid carcinoma or hereditary syndromes associated with thyroid cancer (multiple endocrine neoplasia type 2, Cowden syndrome, familial adenomatous polyposis, Carney complex, and Wermer syndrome); (IV) previous diagnosis of

thyroid carcinoma; (V) age <20 or >70 years; (VI) male sex; and (VII) dysphagia or dysphonia.

Physical examination

Although the predictive value of palpation is limited, a careful physical examination of the thyroid gland and cervical lymph nodes remains an important component of clinical assessment (9). Most malignant TNs are asymptomatic, and the majority of patients are euthyroid. Nevertheless, certain clinical findings may indicate a higher risk of malignancy, including a firm and fixed nodule, nodule size >4 cm, cervical lymphadenopathy, compressive symptoms and signs, and vocal cord paralysis (7,10). According to the literature, the concurrent presence of these features carries an almost 100% positive predictive value for malignancy (11).

LABORATORY EVALUATION

According to current guidelines, the initial laboratory assessment of patients with TNs should begin with measuring serum thyroid-stimulating hormone (TSH), the primary indicator of thyroid functional status (7,12,13). This result determines the subsequent diagnostic pathway, often referred to as the TSH-reflex strategy (Figure 1). If TSH is within the reference range, additional laboratory testing is generally unnecessary.

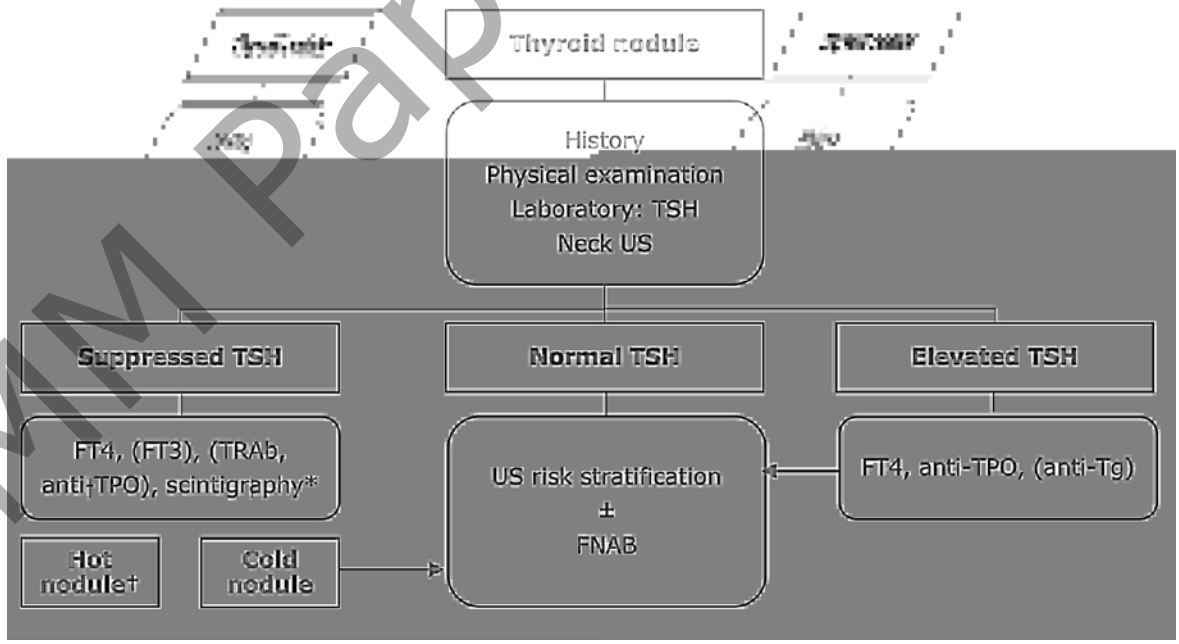

Figure 1. Schematic of thyroid nodule evaluation according to TSH status.

TSH – thyroid-stimulating hormone; FT4 – free thyroxine; FT3 – free triiodothyronine; TRAb – TSH receptor antibodies; anti-TPO – thyroid peroxidase antibodies; anti-Tg – thyroglobulin antibodies; US – ultrasound; FNAB – fine-needle aspiration biopsy.

*In iodine-deficient areas, scintigraphy may also be considered in patients with normal TSH values;

†Malignancy is exceedingly rare in hot nodules; therefore, FNAB is not routinely recommended in such cases.

In cases of suppressed TSH, further evaluation should include free thyroxine (FT4). If FT4 levels are normal, measurement of free triiodothyronine (FT3) is recommended. Depending on the clinical context, testing for TSH receptor antibodies may also be considered to establish the etiology of hyperthyroidism (12,13).

When TSH is elevated, FT4 and thyroid peroxidase antibodies (anti-TPO) should be assessed to determine the underlying cause of hypothyroidism. In patients with clinical or US suspicion of chronic lymphocytic thyroiditis and negative anti-TPO findings, testing for thyroglobulin antibodies (TgAb) may provide additional diagnostic value (12,14).

Measurement of serum Tg is not recommended in the routine evaluation of TNs because of its low specificity. Its use is reserved for the follow-up of patients treated for differentiated thyroid carcinoma (12,14,15).

A similar position applies to calcitonin, which is a highly specific tumor marker for medullary thyroid carcinoma. Although its routine measurement in patients with TNs remains under debate, calcitonin can play an important role in risk assessment in selected patients (12,16). Testing is recommended in cases of a positive family history for this malignancy, strong clinical suspicion, suspicious US findings, indeterminate cytology, or when surgery is already planned. For interpretation, levels >30 pg/mL in women and >34 pg/mL in men may assist in distinguishing medullary thyroid carcinoma from other causes of elevated calcitonin (17).

ULTRASOUND

Neck US, including evaluation of the thyroid gland as well as the central and lateral cervical compartments, should be performed in all patients with suspected TNs (7,12). The risk of malignancy is estimated based on US features of the nodules which, in combination with their

size, determine the subsequent diagnostic pathway, including indications for fine-needle aspiration biopsy (FNAB). US features associated with an increased risk include: taller-than-wide shape, irregular margins, hypoechogenicity, and presence of microcalcifications (18–21). By contrast, US characteristics suggestive of benignity include a predominantly cystic component, a hyperechoic solid nodule, and a spongiform appearance (22,23). In addition, the presence of a thin, uniform halo and peripherally distributed macrocalcifications are considered nonsuspicious US findings, although they do not independently diagnostic benignity (24).
Given the importance of evaluating regional disease spread, US examination should also include assessment of cervical lymph nodes. Although universally accepted criteria for biopsy based solely on sonography are lacking, in daily clinical practice, FNAB is generally recommended for lymph nodes >8 mm that exhibit one or more suspicious features (7,12). These include the presence of microcalcifications, cystic degeneration, loss of normal hilar architecture, marked cortical hyperechogenicity, and abnormal vascular patterns on color Doppler imaging (absence of central flow or predominance of peripheral and chaotic “in–out” flow) (25).

RISK STRATIFICATION SYSTEMS

To reduce interobserver variability and standardize US assessment, several risk stratification systems have been developed under the umbrella term Thyroid Imaging Reporting and Data System (TI-RADS). Currently, the most widely used systems are EU-TI-RADS (European Thyroid Association), ACR-TI-RADS (American College of Radiology), and K-TI-RADS (Korean Society of Thyroid Radiology) (12,26,27). Although they differ in scoring and categorization of sonographic features, none has demonstrated clear superiority, and interobserver agreement is generally comparable across most studies (28–30). Comparative studies suggest that K-TI-RADS provides the highest sensitivity, ACR-TI-RADS the highest specificity, while EU-TI-RADS achieves a balanced trade-off between the two. A further advantage of EU-TI-RADS is its most recent revision in 2023, making it particularly relevant and widely applied in European practice.
Despite their broad implementation, all existing systems have limitations. The most frequently cited are reduced sensitivity in detecting follicular thyroid carcinoma (FTC) and its variants, as well as limited accuracy in distinguishing autonomous nodules (12,31). In addition, variability in defining individual sonographic features and a degree of subjectivity in their interpretation hinder full standardization and comparability of findings across different centers and examiners.

To address these limitations, an international initiative was launched to develop a unified classification termed I-TI-RADS. As an initial step, the International Expert Consensus on Ultrasound Lexicon for Thyroid Nodules was published in 2023, proposing standardized terminology for describing US features (32). In 2025, the first validation study demonstrated high interobserver agreement for most of the proposed descriptors, confirming the practical utility of the lexicon and laying the foundation for further system development (33).

EU-TI-RADS

The revised version, published within the new clinical guidelines of the European Thyroid Association (ETA), retained the five fundamental risk categories (EU-TI-RADS 1–5) while introducing several important modifications aimed at improving diagnostic accuracy and clinical applicability, as summarized in Table 1 (12). In its updated form, the system offers more precise definitions of US features, revised thresholds for FNAB indication, and clearer guidance for classifying nodules with indeterminate findings. It further emphasizes the importance of a flexible, individualized approach tailored to local resources and clinical context.

Table 1. EU-TIRADS classification and FNAB indications (ETA, 2023).

Category	Sonographic description*	Estimated risk (%)	Observed risk in operated cases (%)	FNAB†
EU-TI-RADS 1: Normal gland	No nodules	0	–	No
EU-TI-RADS 2: Benign lesion	Pure cyst; entirely spongiform nodule	0	1,4	No, except for therapeutic purposes
EU-TI-RADS 3: Low risk	Iso-/hyperechoic nodule without suspicious features	2–4	3,5	If >20 mm
EU-TI-RADS 4: Intermediate risk	Mildly hypoechoic nodule without suspicious features	6–17	17	If >15 mm
EU-TI-RADS 5*:* High risk	Presence of ≥1 suspicious feature: - Irregular shape - Irregular margins - Microcalcifications - Hypoechogenicity	26–87	87,7	If >10 mm (or <10 mm with suspicious lymph nodes or extrathyroidal extension)

FNAB – fine-needle aspiration biopsy; EU-TI-RADS – European Thyroid Imaging Reporting and Data System.

*In case of uncertainty about the presence of a suspicious feature, classification as EU-TIRADS 4 is recommended.

†FNAB is indicated regardless of EU-TIRADS category if suspicious lymph nodes are present or if extrathyroidal spread is suspected.

COMPLEMENTARY US TECHNIQUES

Doppler US

Intranodular vascularity was previously considered a marker of increased risk. However, more recent studies suggest it lacks reliable predictive value. In the study by Maddaloni et al., Doppler patterns of overall, peripheral, and intranodular flow did not show significant differences between benign and malignant lesions (34).

With the advent of more sophisticated modalities such as superb microvascular imaging (SMI), a more detailed visualization of microvascularization has become possible, particularly in lesions with slow flow. A meta-analysis by Li et al. (35) demonstrated that combining SMI with conventional US significantly improved diagnostic accuracy (AUC 0.92), supporting its potential role in differentiating lesions with indeterminate US findings.

Elastography

The role of elastography in the evaluation of TNs remains incompletely defined. Although the classical variant of PTC often exhibits high stiffness, other PTC variants and FTC may display elasticity similar to benign nodules (36). Studies assessing the utility of elastography have failed to reach consensus regarding both indications for its use and interpretation of findings (37). Consequently, its contribution to conventional US is not considered sufficient for inclusion in routine evaluation or risk stratification systems.

Contrast-enhanced ultrasound (CEUS)

Several studies have shown that CEUS demonstrates high positive and negative predictive values in assessing the risk of malignancy (38,39). However, results remain heterogeneous, and publication bias has been noted. A meta-analysis by Gao et al. (40), focused on detecting cervical lymph node metastases in PTC, revealed superiority of CEUS over conventional US (AUC 0.92 vs. 0.79). Furthermore, CEUS has proven particularly useful in evaluating the effects of thermal ablation of TNs and in detecting residual or recurrent tumor tissue, thereby aiding clinical decision-making regarding the need for retreatment.

Nonetheless, the use of CEUS remains limited by the lack of standardized criteria, its relatively high cost, and the restricted availability of contrast agents, which are not universally approved for this indication.

CYTOLOGICAL ANALYSIS

FNAB remains the gold standard for excluding malignancy in TNs, with findings classified according to the *Bethesda* System for Reporting Thyroid Cytopathology. The 3rd edition introduced several changes, the most significant of which was the adoption of standardized terminology for each of the six diagnostic categories, along with clearly defined criteria for each (Table 2) (41). The revised estimates of risk of malignancy compared with those in the previous edition, as well as updated management recommendations, are presented and discussed in detail in the following sections:

(I) Nondiagnostic (Bethesda I): Approximately 15% of FNAB samples fall into this category (42). The risk of malignancy is difficult to estimate, as most of these TNs are not surgically removed; however, in operated cases, it is about 13%. A repeat FNAB under US guidance is recommended, yielding a diagnostic result in 60–80% of cases. If the repeated specimen is also Bethesda I, surgical resection should be considered (41).

(II) Benign (Bethesda II): The risk of malignancy is 4% in surgically excised nodules and 1–2% during long-term follow-up. US characteristics form the basis of subsequent surveillance (41).

(III) Atypia of undetermined significance (AUS) (Bethesda III): This category includes findings with cytomorphological changes that cannot be unequivocally classified as benign or malignant. The mean risk of malignancy is 22% in adults and 28% in children (41). Nuclear atypia carries a higher risk compared with other subtypes (architectural, oncocytic, lymphocytic), and in the

latest Bethesda edition, a distinction between nuclear and other types of atypia has been proposed (43,44). Recommended management options include repeat FNAB, molecular testing, lobectomy, or surveillance. In cases of repeated AUS findings or the presence of suspicious features, diagnostic lobectomy is advised, whereas low-risk nodules may be followed (41).

(IV) Follicular neoplasm (Bethesda IV): The risk of malignancy is approximately 30% in adults and 50% in children. In adults, molecular testing may aid in risk assessment, while in children surgical resection is recommended due to the higher malignancy rate (41).

(V) Suspicious for malignancy (Bethesda V): The average risk of malignancy is 74%. Molecular testing may support decision-making regarding the extent of surgery (41).

(VI) Malignant (Bethesda VI): This category comprises cytologically unequivocal malignant tumors, with an average risk of malignancy of 97%. In cases of metastatic findings, additional diagnostic work-up is required to determine the primary tumor site (41).

Table 2. Bethesda System for reporting thyroid cytopathology.

Category	Name	Diagnostic criteria
I	Nondiagnostic	Cyst fluid only; virtually acellular sample; other causes (blood, clotting artifacts, drying artifacts, etc.)
II	Benign	Findings consistent with follicular nodular disease (including adenomatous or colloid nodule), Hashimoto's thyroiditis in the appropriate clinical context, granulomatous (subacute) thyroiditis, others
III	AUS (Atypia of undetermined significance)	AUS – nuclear atypia; AUS – other
IV	Follicular neoplasm	Specify whether oncocytic (Hürthle cell) type
V	Suspicious for malignancy	Suspicion for PTC, MTC, metastatic carcinoma, lymphoma
VI	Malignant	PTC; high-grade FTC; MTC; undifferentiated (anaplastic) carcinoma; squamous carcinoma; carcinoma with mixed features; metastatic malignancy; non-Hodgkin lymphoma; others

AUS – atypia of undetermined significance; PTC – papillary thyroid carcinoma; MTC – medullary thyroid carcinoma; FTC – follicular thyroid carcinoma.

IMMUNOCYTOCHEMISTRY

Among immunocytochemical markers, HBME-1, Galectin-3, and CK19 are most frequently investigated; however, due to their limited sensitivity and specificity, they are not suitable for routine use (45). More recent studies have introduced antibodies targeting specific genetic alterations, such as BRAF^V600E (VE1), Pan-Trk, and ALK; nevertheless, these markers are also not recommended for routine clinical practice (46). In selected situations, staining for calcitonin, Tg, and TTF-1 may be useful, particularly FNAB samples suspicious of metastatic cervical lymph nodes (47).

MOLECULAR TESTING

Approximately 15–30% of TNs are classified as indeterminate FNAB findings (Bethesda III and IV) (48). It is in this group of lesions that molecular testing provides the greatest advancement in differential diagnosis. The aim of testing is more precise risk stratification —either excluding malignancy (rule-out) or confirming malignant potential (rule-in) — thereby substantially reducing the need for diagnostic surgery (49). Analyses are based on the detection of somatic mutations, gene fusions, alterations in gene and microRNA expression, as well as chromosomal copy number variations.

Based on available data from the literature, the most clinically relevant molecular alterations are as follows (49–51): (I) BRAF^V600E - associated with classical PTC, a more aggressive disease course, and poorer prognosis; (II) RAS mutations (HRAS, KRAS, NRAS) - typical of follicular adenomas, FTC, and noninvasive follicular tumors; (III) TERT promoter mutations - strong predictors of poor prognosis. In combination with BRAF V600E, they markedly increase the risk of metastasis and radioiodine refractoriness; (IV) RET and NTRK fusions - more common in younger patients and associated with aggressive PTC variants; (V) PAX8/PPARG and THADA fusions - characteristic of follicular tumors; and (V) miRNA profiles - contribute to distinguishing benign from malignant TNs through specific expression patterns (e.g., miR-146, miR-222).

In recent years, numerous validation studies have confirmed the clinical utility of molecular tests (52–54). Results consistently show that Afirma GSC has the strongest role in the rule-out strategy, ThyroSeq v3 combines both rule-out and rule-in approaches owing to its broad

coverage of mutations and fusions, whereas MPTX has emerged as the most reliable rule-in test. A summary of the diagnostic performance of these assays is provided in Table 3.

Table 3. Commercially available molecular tests and their diagnostic performance in multicenter studies (52–54).

Test	Technology	SN (%)	SP (%)	NPV (%)	PPV (%)	Application
Afirma GSC	RNA-seq, machine learning (expression of >10,000 genes)	91	68	96	47	Best rule-out test (high NPV)
ThyroSeq v3	DNA/RNA-NGS, 112 genes, >120 fusions, CNA	94	82	97	66	Broadest mutation coverage; both rule-out and rule-in
MPTX	Mutation panel (BRAF, RAS, RET, PAX8/PPARG) + miRNA profile	93	90	95	74	Best rule-in test (especially for RAS-positive nodules

SN – sensitivity; SP – specificity; NPV – negative predictive value; PPV – positive predictive value; CNA – copy number alterations.

SCINTIGRAPHY

Scintigraphy with [^99mTc]pertechnetate or [^123I]iodine is selectively applied in patients with suppressed or low-normal TSH levels to confirm autonomous (hyperfunctioning) TNs and thereby avoid unnecessary biopsy (risk of malignancy <1%) (7,12,55). In multinodular goiter, scintigraphy also helps to distinguish lesions that do not require cytological evaluation from those warranting further investigation, as well as to identify candidates for radioiodine therapy. In populations with prior or current iodine deficiency, its use extends to euthyroid patients, since autonomous TNs may be present even without TSH suppression (55).

In TNs with Bethesda III and IV cytology, the value of scintigraphy has further increased with the introduction of new radiopharmaceuticals (Figure 2). [^99mTc]Tc-MIBI is a lipophilic cation

that enters cells and accumulates in mitochondria. Although routinely used for myocardial perfusion assessment and parathyroid imaging, numerous studies have shown that it also accumulates in various tumors, including thyroid neoplasms (56). Schenke et al. (57) demonstrated that low uptake within a TN virtually excludes malignancy. However, positive uptake is also observed in benign lesions (particularly follicular and oncocytic adenomas), resulting in a low positive predictive values (~22%). To improve diagnostic accuracy in these patients, semiquantitative parameters such as the retention index (RI) and washout index (WOind), which account for intranodular [^99mTc]Tc-MIBI kinetics, have been introduced (58). This approach provides better diagnostic performance compared with purely visual analysis (57–59).

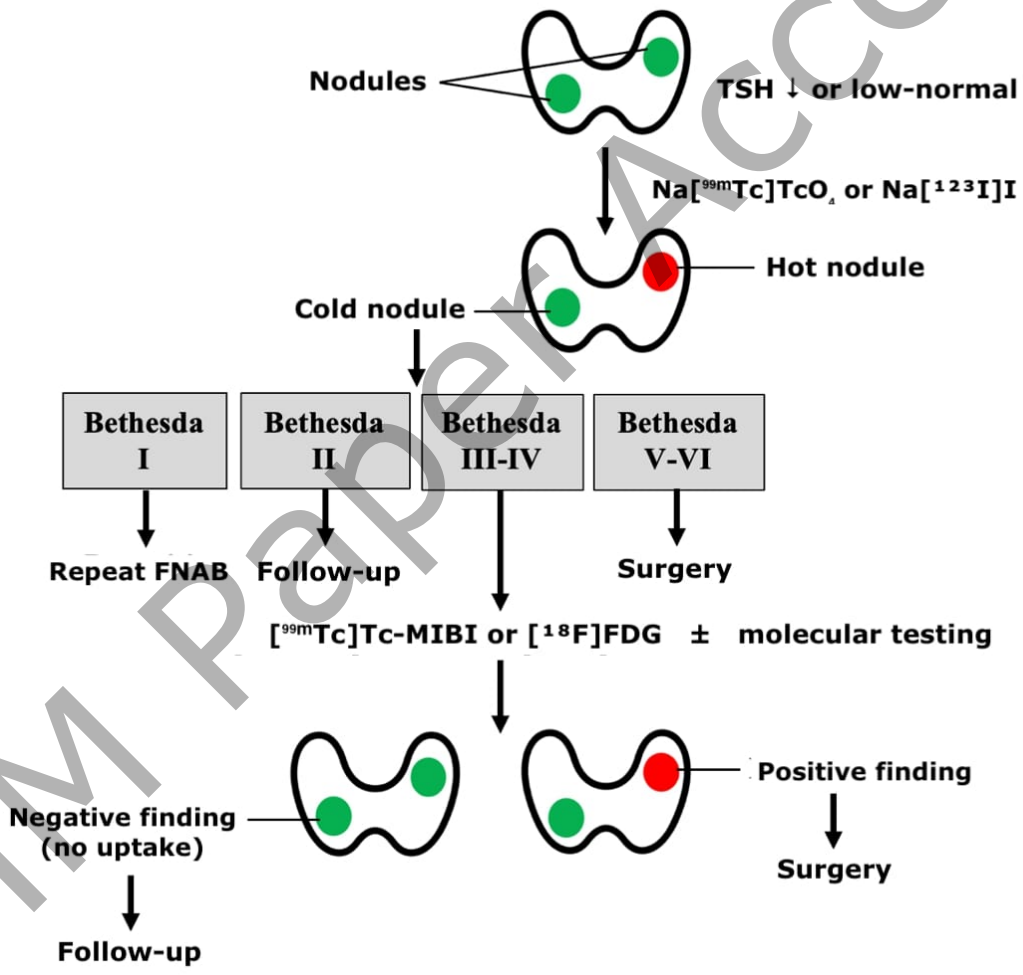

Figure 2. Diagnostic algorithm for TNs.

TSH – thyroid-stimulating hormone; FNAB – fine-needle aspiration biopsy; Na[^99mTc]TcO_4 – sodium pertechnetate; Na[^123I]I – sodium iodide; [^99mTc]Tc-MIBI – technetium-99m–labeled methoxyisobutylisonitrile; [^18F]FDG – fluorine-18–labeled fluorodeoxyglucose.

[^18F]FDG PET/CT is employed for staging, restaging, recurrence detection, and therapy response assessment in various malignancies. Its uptake is based on the overexpression of GLUT transporters and increased hexokinase activity, leading to intracellular tracer retention (60). In cytologically indeterminate TNs, a negative FDG finding virtually excludes malignancy and serves as a reliable rule-out biomarker. However, a positive FDG PET/CT scan is not a reliable rule-in test, as approximately half of PET-positive TNs ultimately prove to be benign. In a multicenter study by de Koster et al. (61), FDG PET/CT reduced the number of unnecessary surgical interventions by approximately 40%. Nevertheless, the authors emphasized that this method is not recommended in Hürthle cell nodules due to physiologically high uptake, even in benign lesions.

ARTIFICIAL INTELLIGENCE (AI) IN THE DIFFERENTIAL DIAGNOSIS OF TNs

The development of AI has markedly advanced diagnostic capabilities in endocrinology, particularly in the differential diagnosis of TNs. The greatest progress has been achieved through the application of machine learning (ML) and deep learning (DL) to US images and cytological preparations, as well as via radiomics and multimodal approaches that integrate clinical, imaging, and molecular data.

The most common applications of AI in US include computer-aided diagnostic systems and radiomics. A recent meta-analysis of DL models demonstrated excellent results, with sensitivity of 91%, specificity of 88%, and an AUC of 0.96 (62). In practice, this indicates that DL generally outperforms traditional ML algorithms. Multicenter prospective studies have shown that AI provides the greatest benefit for less experienced radiologists, enabling them to achieve specificity and accuracy comparable to expert levels, while AI performance itself was comparable to that of the most experienced specialists (63). Commercially available tools such as S-Detect, Koios DS, and AmCAD-UT have already received regulatory approval and are increasingly integrated directly into US devices (64). Nevertheless, it is important to emphasize that therapeutic decisions should not be based solely on AI analysis.

Digital pathology has enabled the development of DL systems for classifying cytological specimens according to the Bethesda system. In multicenter prospective validations, AI models achieved an AUC of approximately 0.95 and significantly improved specificity and accuracy among less experienced pathologists, while yielding results comparable to experts (65). These findings highlight the potential of AI in standardizing and expediting FNAB evaluation, particularly in high-volume centers.

Radiomics allows the extraction of numerous quantitative parameters from US and nuclear imaging. Early studies have shown that such models may achieve diagnostic accuracy comparable to that of experts; however, their broader application remains limited by differences in equipment and a lack of standardization (66). A recent study on PET/CT-incidental nodules demonstrated that AI-based radiomics did not outperform simple parameters such as SUVmax, indicating that further validation is needed (67). The most promising direction for future development remains the integration of AI-based US image analysis with cytological and molecular data.

CONCLUSION

In clinical practice, the differential diagnosis of TNs remains a challenge. A multimodal approach relies on the combination of clinical examination, laboratory testing, scintigraphy, US-based risk stratification, and cytological evaluation. Although FNAB and the Bethesda system remain the gold standard, the high proportion of indeterminate results necessitates the use of complementary methods. Molecular testing, functional imaging modalities, and novel US techniques significantly enhance risk assessment and reduce unnecessary surgical interventions. The development of AI offers the potential for standardization and personalization of diagnostic strategies. However, its routine implementation still requires further validation through multicenter prospective studies. By integrating classical and modern methods, a more precise and individualized evaluation of patients with thyroid nodules can ultimately be achieved.

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