Review Article

The diagnosis and management of thyroid nodules: Consensus statement of the Indian Thyroid Society

ABSTRACT

Thyroid nodules are a common occurrence in the Indian population. The current management involving an individualized approach is increasingly becoming relevant instead of a broad diagnostic and management algorithm. The consensus statements derived in this article aim to provide a summary of the current medical evidence for the diagnosis and management of thyroid nodules, which assists in optimizing recommendations in the Indian setting. The task force of experts has provided inputs to address specific clinical questions in this consensus. The statements are formulated after a thorough analysis of several published studies and guidelines to address the screening, diagnosis, and management of thyroid nodules. A well-defined grading system is used to appraise the evidence and grade the strength of recommendations. This guideline covers risk stratification of thyroid nodules (differentiating benign from malignant lesions) and a guide to the use of fine-needle aspiration cytology to improve definitive management. The guideline covers evidence-based recommendations for the management of benign, cytologically indeterminate, and malignant thyroid nodules. The panel has also touched upon the aspects of nondiagnostic thyroid nodule management and intraoperative neuromonitoring. These evidence-based expert consensus statements can provide useful and practical insights to aid the practicing clinician.

Keywords: Benign thyroid nodules, Bethesda system, cytologically indeterminate thyroid nodules, fine-needle aspiration, Indian Thyroid Society, intraoperative neuromonitoring, malignant thyroid nodules, molecular testing, nondiagnostic thyroid nodules, thermal ablation, thyroid cancer, thyroid cytology, thyroid nodules, Thyroid Imaging Reporting and Data System, ultrasonography

INTRODUCTION

A thyroid nodule is a lesion within the thyroid gland that is radiologically distinct from the surrounding thyroid parenchyma, which may be palpable clinically.[1] Thyroid nodules are commonly reported to occur in women, increasing with age, in those with iodine deficiency and with a history of radiation exposure.[2]

The widespread availability and use of sensitive imaging techniques have led to an increase in the incidence of thyroid nodules over time. Most thyroid lesions are benign and asymptomatic, which do not require active intervention and may be followed up periodically. Risk of malignancy increases in high-risk thyroid nodules based on ultrasonography (US) evaluation and US-guided fine-needle aspiration cytology (FNAC) findings.

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As stated in the recently published European Thyroid Association (ETA) 2023 clinical practice guideline, the actual prevalence of cancer ranges from 1% to 5% in unselected thyroid nodule populations. This prevalence may vary based on the population under evaluation and selection criteria, such as the inclusion of papillary microcarcinomas. Many of these thyroid nodules harbor papillary microcarcinoma and follow a very indolent course, allowing for conservative management approaches such as active surveillance and the use of minimally invasive techniques.[3]

With the advent of high-resolution US, there has been an overdiagnosis of benign and malignant lesions, resulting in an increased number of thyroidectomies without significant lowering of thyroid cancer mortality. Therefore, a more cost-effective approach that considers risks and prioritizes the patient's comfort has been a necessity.[3]

Objective

The aim of this consensus is to update recommendations for the appropriate diagnosis, classification, risk stratification, and management of thyroid nodules.

Expert panel and consensus process

The task force comprised experts in the field of endocrinology and thyroid disease. Several published studies and guidelines were explored to address the screening, diagnosis, and management of thyroid nodules. This document provides much-required insights and useful, practical, and accurate guidance that aids a practicing clinician. The guideline was developed through a series of e-mails, conference calls, and face-to-face meetings. The task force prepared the initial draft with the assistance of a medical writer, and it was reviewed and commented on by members of the Indian Thyroid Society.

METHODS

The sections and recommendations addressed in the guideline were formulated based on input from task force members and insights from previous trials and guidelines. The task force members employed a well-defined grading system [Table 1] for the critical appraisal of evidence and grading strength of recommendations.

Table 1: Level of evidence and grading strength of recommendations

	Description
Level of evidence	
Level A	Data derived from multiple randomized trials or meta-analyses or evidence-based clinical practice guidelines
Level B	Data derived from a single randomized trial or large nonrandomized trial
Level C	The consensus of opinion of experts or small studies, retrospective studies or registries or narrative/literature reviews
Level D	Data derived from clinical experience
Class of recommendations	
Class I	Evidence and or general agreement that a given treatment or procedure is beneficial, useful or effective. It is recommended
Class IIa	Evidence is in favor of efficacy/usefulness and should be considered
Class IIb	Efficacy/usefulness is less well established and recommendations may be considered
Class III	Evidence and or general agreement that a given treatment or procedure is not beneficial, useful, or effective and in some cases may cause harm. Not recommended

CLINICAL QUESTION

Prevalence of thyroid nodules in the Indian population

How prevalent is the occurrence of thyroid nodules among the Indian population?

In India, an estimated 42 million people suffer from thyroid diseases, and approximately 8.5% of the population have a thyroid nodule.[4] The prevalence of thyroid nodules can vary based on the mode of discovery, with percentages ranging from 2% to 6% when identified on palpation, 19%–35% through ultrasound, and 8%–65% based on autopsy data.[5]

As per a review conducted by Indian authors, the prevalence of thyroid nodules detected through palpation was reported to be <5%, but the identification increased to around 65% with the use of an ultrasound in a population-based study. On ultrasound screening, around 20%–48% of patients had additional thyroid nodules.[6] The number of clinically significant thyroid nodules (>1 cm) is much lower than the clinically insignificant thyroid nodules (<1 cm).

Reports have confirmed that thyroid nodules are commonly found in regions with iodine deficiency, among advancing

age groups, and among females.[6] Studies conducted on the Indian population have demonstrated a prevalence of 18.9% in iodine-sufficient areas and 80% in areas with iodine deficiency.[6]

A study was conducted to generate epidemiological data in the Indian population regarding the prevalence of thyroid disorders. A retrospective analysis of cytomorphology of fine-needle aspiration (FNA) cytology material of 206 patients presenting with thyroid nodules was included. Findings showed that the most affected age group for thyroid nodules was 31–40 years. Female patients constituted 93.4% of the cases, outnumbering male patients by a ratio of 1:14. This indicates a higher prevalence of thyroid nodules in females compared to males.[4]

According to a study conducted in South India, the prevalence of clinically palpable, solitary thyroid nodules (STN) was found to be 19.2%. The majority were females (86.7%), and the maximum number of cases (36%) belonged to the age group of 21–30 years. All patients had swelling of the thyroid region, and FNAC conducted showed that majority had follicular neoplasm (FN). Reports have shown that solitary nodule has a higher risk of being malignant (10%–20%) than the multiple palpable nodules of a multinodular goiter (MNG) (5%).[7]

Another study conducted in South India was based on the review of case records of all patients who were operated for STN. Around 350 patients were operated for various thyroid diseases during the study period. Clinically detected STN was the most common occurrence, accounting for 162 (46%) patients. The next common entity was MNG, noted in 138 (39.6%) patients. Majority of the patients with STN were females (n = 113, 69.7%), with a mean age of 36.8 ± 13.3 years. Around 39.7% of clinically detected STNs were reported as malignant in the final histopathological examination (HPE). The study shows that the incidence of malignancy in STNs is high.[8]

Consensus statement

- The prevalence of thyroid nodules is high within the Indian population, especially in regions with iodine deficiency, mainly among women, majorly STN, with solitary nodules having a higher risk of being malignant (B/IIb).

CLINICAL QUESTIONS

Causes and evaluation of thyroid nodules

Which thyroid nodules require clinical evaluation?

Considering the etiology of thyroid nodules is important, since it may assist in evaluation. Further, a thyroid nodule can be either solitary or multinodular, and they may either be benign or malignant, with the benign variety forming the majority. Nodules with benign etiology include colloid nodules, hyperplastic nodules, cystic nodules, Hashimoto's thyroiditis, follicular adenoma, and Hurthle cell adenoma, whereas, the malignant causes include differentiated thyroid cancer, anaplastic thyroid cancer, lymphoma, and metastatic cancer.[1,6]

Table 2: Factors suggesting an increased risk of malignant potential of thyroid nodules[2]

History of head and neck irradiation
Family history of medullary thyroid carcinoma, multiple endocrine neoplasia type 2, or PTC
Age <14 or >70 years
Male sex
Growing nodule
Firm or hard consistency
Cervical adenopathy
Fixed nodule
Persistent dysphonia, dysphagia, or dyspnea

PTC: Papillary thyroid carcinoma

Clinical evaluation is essential for all thyroid nodules larger than 1 cm, both palpable and nonpalpable (including incidentalomas discovered during imaging). Nodules smaller than 1 cm should be evaluated based on individual risk factors. The focus of the clinical evaluation is to differentiate malignant thyroid nodules from benign ones. Some classical features [Table 2] of thyroid nodules are usually suspicious and suggest malignancy and indicate further evaluation.[1]

What are the initial approaches for the evaluation of patients for thyroid nodules?

The initial evaluation of any patient suspected of nodular thyroid disease should include the combination of personal and family history, physical examination, evaluation of thyroid function, and ultrasound of the neck.[3]

The patient's history should include assessing risk factors. A careful history is required to elucidate past thyroid disease, history of malignancy, childhood exposure to head or neck irradiation, total body irradiation, family history of certain thyroid cancers or syndromes (Cowden's syndrome, familial polyposis, Carney complex, multiple endocrine neoplasia 2, and Werner syndrome), or an enlarging nodule/rapid nodule growth.[5]

The physical examination should involve thoroughly inspecting and palpating the thyroid gland and cervical lymph nodes for volume and consistency, as well as nodular features such as location, size, number, tenderness, consistency, and attachment to surrounding structures. It should be noted that the nodules smaller, usually <1 cm in size, and located posteriorly or substernally might be difficult to palpate.[2,5]

Physical examination may not be able to detect small-differentiated thyroid cancers as they often lack alarming characteristics. However, a solitary or dominant thyroid nodule, which may be firm or hard, could suggest an increased risk of malignancy. Hence, the American Association of Clinical Endocrinologists, Associazione Medici Endocrinologi (Italian Association of clinical endocrinologist), and ETA (AACE/AME/ETA) Guidelines suggest careful palpation of the thyroid gland and the anterior and lateral nodal compartments of the neck. The factors suggestive of increased risk of malignant potential are mentioned in Table 2.[2]

What are the signs and symptoms to look for in aggressive thyroid nodules?

Rapidly progressive growth of nodules, over weeks or months, may indicate suspicion of malignancy.[2]

The clinician should also examine for signs of hypothyroidism or hyperthyroidism. Other possible signs and symptoms observed in patients are as follows:[2]

- Sudden pain due to hemorrhage in a cystic nodule
- Choking sensation, cervical tenderness or pain, dysphagia, or hoarseness may be due to thyroid disease
- Slow-onset cervical symptoms and signs due to the compression of vital structures of the neck or upper thoracic cavity usually occur if thyroid nodules are embedded within large goiters
- Tracheal compression (cough and dysphonia) may suggest an underlying malignant lesion in the absence of multinodular goiter
- Absence of local symptoms does not rule out a malignant tumor
    - Differentiated thyroid carcinomas only rarely cause airway obstruction
    - Vocal cord paralysis or esophageal symptoms.

Consensus statement

- Initial evaluation for suspected cases should include the patient's personal history of thyroid disease, malignancy, irradiation, and family history of cancers or the presence of thyroid nodules (A/I)
- A careful physical examination of the thyroid gland and cervical lymph nodes should be performed. It is necessary to record the location, consistency, size, tenderness, and volume of thyroid nodules (A/I)
- The associated signs and symptoms should be recorded. While most nodules are asymptomatic, the absence of symptoms cannot be a criterion to rule out malignancy (A/I).

CLINICAL QUESTIONS

Diagnostic methods for thyroid nodules

What are the initial laboratory tests and role of thyroid scintigraphy in the evaluation of patients with thyroid nodules?

The AACE/AME/ETA Guidelines suggest measuring serum thyroid-stimulating hormone (TSH) in patients with thyroid nodules. If the TSH level is outside the reference range, the serum levels of free thyroid hormones (free thyroxine [FT4] and free triiodothyronine [FT3]) and thyroid peroxidase antibodies (TPOAbs) or anti-TSH-receptor antibody should be the second diagnostic step. The guideline suggests following the strategy for most patients with thyroid nodules:[2]

1. Serum TSH level within normal limits: No further testing (unless there is suspicion of central hypothyroidism)
2. Increased serum TSH: Test FT4 and TPOAbs to evaluate for hypothyroidism
3. Decreased serum TSH: Test FT4 and FT3 to evaluate for hyperthyroidism.

Another review suggests that if TSH is suppressed, then total T3 and FT4 should be measured. If both total T3 and FT4 levels are elevated, then a radionucleotide scan (thyroid scintigraphy) should be performed.[6] The ETA 2023 guideline suggests TSH measurement, if it is suppressed than determining FT4 is recommended. If FT4 is normal, FT3 should be measured.[3]

As per the American Thyroid Association (ATA), a serum TSH level should be obtained with the discovery of a thyroid nodule >1 cm in any diameter. A subnormal serum TSH indicates performing a radionuclide thyroid scan (thyroid scintigraphy) to document whether the nodule is hyperfunctioning ("hot" [tracer uptake is greater than the surrounding normal thyroid]), isofunctioning ("warm" [tracer uptake is equal to the surrounding thyroid]), or nonfunctioning ("cold" [has uptake less than the surrounding thyroid tissue]). Cold nodules on thyroid scintigraphy have a high risk of malignancy and will require US-guided FNAC evaluation. There is no role of thyroid scintigraphy in the current scenario in patients with either increased or normal TSH.[9]

Consensus statement

- Serum TSH should be measured during the initial evaluation of a patients with a thyroid nodule. If TSH is suppressed, then total T3 and FT4 should be measured. If T3 and FT4 levels are also elevated, then a radionuclide scan (thyroid scintigraphy) should be performed (A/I)
- Thyroid scintigraphy is not recommended as the initial imaging evaluation in cases with normal or elevated TSH levels (A/I).

What is the role of ultrasonography in the detection of thyroid nodules?

US is the first line of investigation for the evaluation of nodular thyroid

disease. All patients with clinically suspected nodular thyroid disease or incidentally detected nodules with other imaging modalities should undergo thyroid and neck US. The presence, location, size, and features of nodules and thyroid lobes should be assessed. The details of the thyroid US report are provided in Table 3.[3]

US should also be performed in patients with low serum TSH levels who have undergone radionuclide thyroid scintigraphy suggesting nodularity.[9]

The characteristic findings of malignancy in US are solid compositions, microcalcification, irregular margin, hypoechogenicity, taller than wide shape, absent halo, and an increase in blood flow. Therefore, a US-guided Thyroid Imaging Reporting and Data System (TI-RADS) has been proposed for risk stratification of thyroid nodules to improve definite management.[10]

The TI-RADS is a reliable, noninvasive method to identify which nodules warrant FNA based on their categorization as benign, minimally suspicious, moderately suspicious, or highly suspicious for malignancy. Table 4 presents these features arranged as per the five lexicon categories, determining the nodule's American College of Radiology (ACR) TI-RADS level, which ranges from TR1 (benign) to TR5 (high suspicion of malignancy).[11]

Consensus statement

- Thyroid and neck US should be performed in all patients with clinically suspected nodular thyroid disease or incidentally detected nodules. The location, size, and features of nodules and thyroid lobes should be assessed (A/I)
- A US-guided TI-RADS [Table 4] is suggested to be used for risk stratification of thyroid nodules (to differentiate benign from malignant lesions) and to identify which nodules warrant FNA in order to improve definite management (A/I)
- In case of multinodularity, details of all nodules with suspicious features should be described (A/I).

What is the role of fine-needle aspiration, thyroid cytology, and molecular testing in the diagnosis of thyroid nodules?

Fine-needle aspiration

FNA can be indicated after obtaining a clinical, biochemical, and US evaluation along with a dialog with the patient. It is strongly suggested that FNA should be performed under US guidance.[3]

A guide to indications for FNA cytology includes many US risk-stratification systems (RSSs), which have their own cutoffs, and a continuous debate exists on the optimum threshold.[3] A study was conducted to assess the performances of five internationally endorsed sonographic classification systems (those of the ATA, AACE, ACR, ETA, and the Korean Society of Thyroid Radiology) in identifying nodules whose FNAs can be safely deferred and to estimate their negative predictive values (NPVs). Application of the FNA criteria would have reduced the number of biopsies performed by 17.1%–53.4% (17.1% using Korean TI-RADS, 30.7% using European-TI-RADS, 34.9% applying AACE/ACE/AME, 43.8% for ATA, and 53.4% with ACR TI-RADS). It was found that the ACR TI-RADS allowed the largest reduction with the lowest false negative rate (FNR) (NPV = 97.8%; 95% confidence interval [CI] = 95.2%–99.2%). The rate of missed carcinomas in nodules >1 cm was low comprising between 2.2% for ACR TI-RADS and 4.1% for ATA TI-RADS. Thus, all RSSs were noted to be effective to reduce the number of unnecessary FNAs.[12]

The ETA 2023 guideline suggests that FNA can be indicated based on TI-RADS, and factors that may influence this choice are described in Tables 4 and 5, respectively. FNA should be repeated in case of a first nondiagnostic sample, a Bethesda class III cytology, or a discrepancy between US risk score (i.e., high risk) and cytological findings (benign cytology).[3]

Core-needle biopsy

Core-needle biopsy (CNB) performed properly under ultrasound guidance can be useful in providing additional

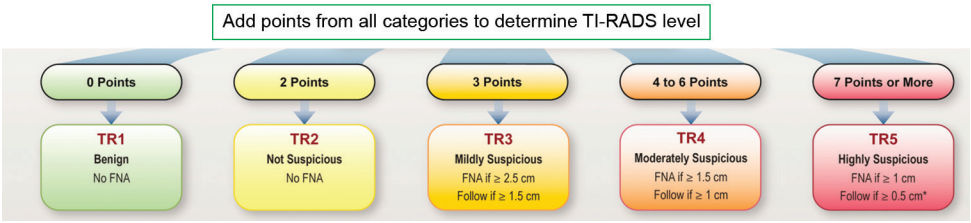
Table 3: Elements of thyroid ultrasound reporting in nodular thyroid disease[3]

Thyroid lobes	Nodules	Description of discrete lesions	Number of nodules described	Presence of pathological lymph nodes
Echogenicity Size (three diameters and volume) Presence of substernal extension or compression of cervical structures	Size (three diameters and volume) Location (according to the three axes) Echogenicity Composition Suspicious and nonsuspicious signs if present Possible extrathyroidal extension	Nodules larger than 10 mm Nodules between 5 mm and 10 mm with suspicious signs	The largest one Nodules with suspicious signs if the number of nodules is >3 in a lobe	Location, three diameters, features

Suspicious ultrasound characteristics: Microcalcifications, irregular margins, nonparallel orientation, marked hypoechogenicity of the solid part. Nonsuspicious ultrasound characteristic: Thin halo, macrocalcification (specify rim calcification)

Table 4: American College of Radiology thyroid imaging and reporting data system for risk stratification and indication of fine-needle aspiration cytology[11]

Composition		Echogenicity		Shape		Margin		Echogenic foci	
Cystic or almost completely cystic	0 point	Anechoic	0 point	Wider-than-tall	0 points	Smooth	0 points	None or large comet-tail artifacts	0 points
Spongiform	0 point	Hyperechoic or isoechoic	1 point	Taller-than-wider	3 points	Ill defined	0 points	Macrocalcifications	1 point
Mixed cystic and solid	1 point	Hypoechoic	2 points			Lobulated or irregular	2 points	Peripheral (rim) calcifications	2 points
Solid or almost completely solid	2 points	Very hypoechoic	3 points			Extra-thyroidal extension	3 points	Punctate echogenic foci	3 points



information to FNA biopsy in selected cases of thyroid or neck masses when repeated FNA biopsy cytology is inadequate. US-guided CNB should be considered a complementary investigational tool and not as an alternative to FNA biopsy.[2,3]

Consensus statement

- Indication for FNA for thyroid nodules should be based on the combination of clinical factors, laboratory evaluation, and US risk stratification and performed under US guidance (A/I)
- The indication for FNA should be based on the following size cutoffs (A/I):
  - TR3: If nodules ≥2.5 cm (mildly suspicious)
  - TR4: If nodules ≥1.5 cm (moderately suspicious)
  - TR5: If nodules ≥1 cm (highly suspicious)
- FNA should be repeated in case of a first nondiagnostic sample, a Bethesda class III cytology, or a discrepancy between US risk score (high risk) and cytological findings (benign cytology) (A/I)
- US guided core-needle biopsy can be considered an additional procedure to FNA biopsy in selected cases (A/I).

Thyroid cytopathology

A strategic system proposed by the Bethesda System for Reporting of Thyroid Cytopathology (TBSRTC) is accepted worldwide and can be incorporated to improve the evaluation and categorization of thyroid nodules. The Bethesda system classifies thyroid FNA findings into six categories with specific malignancy risks and guides in making further therapeutic decisions.[10]

Table 5: Criteria other than size and ultrasonography risk level that strengthen or weaken the indication for fine-needle aspiration[3]

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

FDG: Fluorodeoxyglucose, FNA: Fine-needle aspiration, MEN2: Multiple endocrine neoplasia type 2, MIBI: Methoxy-isobutyl-isonitrile, MNG: Multinodular goiter

The advantages of this system include well-defined rate of malignancy (ROM) rates, management algorithms linked to each diagnostic category, and integration of molecular tests in the reporting. The TBSRTC system can be integrated into the local setting, with demographic-based local calculation of ROM for recording the local thyroid cancer incidence.[3]

The latest TBSRTC 2023 third edition report recommends that every thyroid FNA report should begin with 1 of the 6 diagnostic categories. This report addresses one of the

limitations of the prior editions that had led to confusion with alternative names for three of the diagnostic categories. The 2023 report recommends a single designation for each of the six categories, discontinuing the previously used terms. The report suggests the use of names of the categories (and not just their numerical designations) for reporting results and publishing scientific investigations to avoid confusion with the TI-RADS and other reporting systems. Each of the categories has an implied cancer risk that links it to an evidence-based clinical management guideline. The revised and updated range and average ROMs are depicted in Table 6.[13]

An Indian study aimed to establish a correlation between the intermediate Bethesda categories of thyroid lesions and the corresponding TI-RADS categories during the assessment of ROM. The study included patients aged 18 years or older had STNs, and all cases were triaged using both TI-RADS and TBSRTC 2017. The diagnostic performances were compared with subsequent paraffin sections to evaluate ROM. TI-RADS and TBSRTC systems demonstrated good concordance in the evaluation of benign thyroid nodule (BTN) lesions (Category 2-II). However, discordance was reported in follicular lesions (Category 4-IV). A moderate agreement between the two RSSs was reported based on the kappa value of 0.411. The authors concluded that careful application of both grading systems is important for proper segregation of thyroid nodules and facilitates effective clinical and surgical management.[10]

Another Indian study has shown that FNAC and TI-RADS are both highly sensitive (80%) in diagnosing malignant thyroid nodules, but FNA is more specific (90%) and accurate tests (85%) in identifying thyroid cancer.[14]

Consensus statement

The Bethesda System for Reporting of Thyroid cytopathology (TBSRTC) 2023 recommends that every thyroid FNA report should begin with 1 of the 6 diagnostic categories. The BSRTC system categories have an implied cancer risk, which is linked to recommended clinical management.

I. Nondiagnostic: Repeat FNA with ultrasound guidance
II. Benign: Clinical and ultrasound follow-up
III. Atypia of undetermined significance (AUS): Repeat FNA molecular testing, diagnostic lobectomy, or surveillance
IV. Follicular neoplasm: Molecular testing, diagnostic lobectomy
V. Suspicious for malignancy: Molecular testing, lobectomy or near-total thyroidectomy
VI. Malignant: Lobectomy or near-total thyroidectomy.

Molecular testing

Molecular testing in FNAC samples can help in the interpretation of the indeterminate thyroid nodule, which usually presents a management dilemma. FNAC samples can be tested for a panel of mutations which includes BRAF (V600E), RAS, RET/PTC, and PAX8/PPARγ, which can help in improving the diagnostic accuracy of FNAC. As these mutations are known drivers associated with thyroid cancer, clinical management for a significant proportion of patients with indeterminate cytology can be refined.[6] Molecular testing can help in avoiding diagnostic surgery and can identify patients with a high likelihood of malignancy who need surgical treatment.[3] Various newer molecular techniques, such as the determination of the presence of mutations from circulating cell-free DNA (cfDNA), have been explored to help in diagnosis of indeterminate thyroid nodules.[15]

The ATA recommends that for indeterminate cytology (atypia of undetermined significance [AUS]/follicular lesion of undetermined significance [FLUS], FN, and SUSP), and especially for suspicious for malignancy cytology, mutational testing for BRAF or the seven-gene mutation marker panel (BRAF, RAS, RET/PTC, PAX8/PPARc) may be considered if it is expected to alter surgical decision-making.[9]

The use of liquid biopsy (cfDNA and RNA) in malignancy could be important. Several reports on thyroid nodules have demonstrated/detected individual somatic driver mutations like BRAF V600E from cfDNA.[15]

A study was conducted by Indian researchers to analyze cfDNA levels in patients with thyroid nodules to explore the possibility of establishing a cutoff for the identification of malignancy. A very strong agreement was reported between cfDNA-based classification and histopathology-based classification of benign and malignant nodules (Cohen's kappa = 0.94; $P < 0.001$). The authors concluded that plasma cfDNA estimation could help differentiate malignant from BTNs.[15]

Another study by Tarafdar *et al*. showed that the presence of longer DNA strands circulating in plasma of patients presenting with thyroid nodules could be considered a marker for thyroid cancer. Findings showed that CfDNA integrity index was higher in differentiated thyroid carcinoma patients (median = 0.45, 95% CI = 0.36–0.52) than in subjects with benign nodules (median = 0.32, 95% CI = 0.27–0.39).[16] A study that was conducted to determine the expression of long noncoding RNA (lncRNA) in plasma of patients with thyroid nodules showed that PVT1 expression from plasma could help in differentiating malignant from BTNs.[17]

Table 6: Bethesda system for reporting of thyroid cytopathology 2023 categories with an implied cancer risk that links it to a recommended clinical management[13]

Diagnostic category	ROM[a], mean (%) (range)	Usual management[b]
Nondiagnostic		
Cyst fluid only	13 (5–20)	Repeat FNA with ultrasound guidance
Virtually acellular specimen		
Other (obscuring blood, clotting artifact, drying artifact, etc.)		
Benign		
Consistent with follicular nodular disease (includes adenomatoid nodule, colloid nodule, etc.)	4 (2–7)	Clinical and ultrasound follow-up
Consistent with chronic lymphocytic (Hashimoto) thyroiditis in the proper clinical context		
Consistent with granulomatous (subacute) thyroiditis		
Other		
AUS		
Specify if AUS-nuclear atypia or AUS-other	22 (13–30)	Repeat FNA, molecular testing, diagnostic lobectomy, or surveillance
Follicular neoplasm		
Specify if oncocytic (formerly Hurthle cell) type	30 (23–34)	Molecular testing, diagnostic lobectomy
Suspicious for malignancy		
Suspicious for PTC	74 (67–83)	Molecular testing, lobectomy, or near-total thyroidectomy
Suspicious for medullary thyroid carcinoma		
Suspicious for metastatic carcinoma		
Suspicious for lymphoma		
Other		
Malignant		
PTC	97 (97–100)	Lobectomy or near-total thyroidectomy
High-grade follicular-derived carcinoma		
Medullary thyroid carcinoma		
Undifferentiated (anaplastic) carcinoma		
Squamous cell carcinoma		
Carcinoma with mixed features (specify)		
Metastatic malignancy		
Non-Hodgkin lymphoma		
Other		

[a]ROM estimates are skewed by selection bias, because many thyroid nodules (especially those diagnosed as benign or atypia of undetermined significance) might not undergo surgical excision, [b]Actual management could depend on other factors (e.g., clinical, ultrasound findings), in addition to the FNA interpretation. FNA: Fine-needle aspiration, ROM: Rate of Malignancy , AUS: Atypia of undetermined significance, PTC: Papillary thyroid carcinoma

Another research demonstrated that the expression of plasma lncRNAs of PVT1, MALAT1, and BANCR was found to be significantly different between benign and malignant nodules ($P < 0.001$).[18] These newer molecular techniques using liquid biopsy for detection of driver mutations, cfDNA concentration, lncRNA, and miRNA expression need further validation in larger cohorts in multicentric trials to be included in clinical practice.

Consensus statement

- Molecular testing such as analyzing cell-free DNA and long noncoding RNA levels in patients with thyroid nodules can be useful molecular noninvasive diagnostic markers to help differentiate benign from malignant thyroid nodules, including in those presenting with indeterminate thyroid nodules (B/I).

CLINICAL QUESTIONS

Management of thyroid nodules

The possible reports from the cytopathologist are benign, malignant/suspicious, indeterminate, and nondiagnostic.[1]

How are benign thyroid nodules managed?

The benign reports could be either colloid goiter, lymphocytic thyroiditis, or a benign cyst. Subjects with benign cytology are considered true negative if they are followed up for a period of at least 2 years – this will allow identification of those with changing symptoms for a repeat fine-needle aspiration biopsy, and true negativity is confirmed if a diagnosis of thyroid neoplasia has not been made after a 2-year follow-up.[1]

Nodules benign by fine-needle aspiration biopsy

Levothyroxine suppressive therapy

Levothyroxine suppression therapy to shrink nonmalignant nodules may slow nodule growth and prevent the appearance of new nodules. However, this therapy is less common due to the associated disadvantages, such as the need for long-term suppression, posttherapy regrowth, risk of atrial fibrillation/cardiac arrhythmias, and reduction in bone mineral density.[19]

Evidence from meta-analyses has suggested that thyroid hormone suppressive therapy reduces the volume of BTNs by more than 50%.[20,21]

An Indian study has shown that thyroxine therapy may have a role in reducing and arresting further growth of benign thyroid swellings. The majority of patients showed a decreasing trend in the volume of thyroid after 1 year of thyroxine therapy, even though the amount of reduction was not statistically significant. The rate of decrease in thyroid volume was found to be significantly higher in patients with higher TSH values.[22]

Data have demonstrated variable TSH suppression in many studies, ranging from suppression of TSH to <0.2 mIU/L to <0.1 mIU/L. However, TSH suppression to this degree is significantly associated with an increased risk of cardiac arrhythmias and osteoporosis, as well as adverse symptomatology. Therefore, levothyroxine suppressive therapy, although effective in nodule volume reduction, increases the risk of adverse consequences.[9]

The ATA 2016 guideline has not recommended routine TSH suppression therapy for BTNs in iodine-sufficient populations.[9]

The AACE/AME/ETA Thyroid Nodule Guidelines have suggested that levothyroxine therapy or iodine supplementation may be considered in young patients with small nodular goiter and no evidence of functional autonomy, and be avoided in those with large thyroid nodules or longstanding goiters; in patients with low-normal TSH levels; in postmenopausal women; in men older than 60 years; and in patients with osteoporosis, cardiovascular disease, or systemic illnesses.[2]

Consensus statement

- Routine TSH suppression therapy for benign thyroid nodules is not necessary (A/I)
- Levothyroxine therapy or iodine supplementation can be considered in young patients with small nodular goiter and depends on the decision by the treating physician and an endocrinologist (A/I).

Surgery for benign thyroid nodules

Surgical removal may be needed for benign nodules if they are causing pressure or structural symptoms.[5]

The ATA suggests that surgery may be considered for growing nodules that are benign after repeating FNA if they are large (>4 cm), causing compressive or structural symptoms, or based upon clinical concern. Whereas benign nodules with no change in size should be regularly monitored without intervention.[9]

The AACE/AME/ETA Thyroid Nodule Guidelines suggest that benign uninodular goiter can be resected with lobectomy plus isthmectomy and for multinodular goiter is (near) total thyroidectomy.[2]

The Endocrine Society of India management guidelines have indicated that the choice of surgery (total or hemi- or subtotal thyroidectomy) in subjects with benign cytology has often been a source of debate.[1]

Consensus statement

- Surgery for benign thyroid nodules can be considered if they are growing and causing pressure or symptoms. The choice of surgery (total or hemi- or subtotal thyroidectomy) depends on the decision by the treating physician and an endocrinologist (A/I).

Ultrasonography-guided minimally invasive procedures

Percutaneous ethanol injection

Ethanol injection into nodules may be useful, especially for the symptomatic cystic nodules.[19]

A long-term study has shown that percutaneous ethanol injection (PEI) can cure most recurrent cystic lesions of the thyroid. After a follow-up of 5 years, PEI treatment in cystic nodules showed a volume reduction >75% versus baseline in 86.2% of cases. An improvement of local symptoms was also observed in 91.4% of cases. The study showed that treatment with PEI led to a marked volume reduction and normal serum TSH levels in majority of autonomously functioning nodules and toxic nodules with volume <5.0 mL.[23]

An Indian study has shown that PEI was safe and effective for the treatment of simple cystic thyroid nodules. The response rate to PEI in simple cystic nodules at the end of the study was 92.86% (39/42 patients) as compared to 44.44% (8/18 patients) for complex cystic nodules ($P < 0.001$). Simple cystic nodules had significantly higher response rates to PEI at 1-, 3-, 6-, and 9-month follow-up, with significantly lower residual volumes. lower residual volumes, whereas, PEI in patients with complex

cystic thyroid nodules were associated with a lower rate of remission, increased recurrence, and need for repeated PEI.[24]

Reports have shown that PEI may not be useful for hyperfunctioning nodules or nodular goiters because of a high recurrence rate or availability of alternative treatment options.[2]

Consensus statement

- PEI is safe and effective for volume reduction in thyroid cysts and thus can be considered as the treatment of choice for simple cystic thyroid nodules (B/I).

Thermal ablation

Thermal ablation (TA), including radiofrequency ablation (RFA), microwave ablation (MWA), laser ablation (LA), and high-intensity focused ultrasound, is generally reported to be applied for solid or mixed BTNs. Several studies have shown that TA for BTNs has been widely utilized across many countries with good efficacy and safety. Although not all BTNs were found suitable for TA therapy, long ablation time or multiple ablation operations are required for the nodules with large sizes. Patients are concerned about nodule regrowth in BTNs after TA.[25]

A recent 2023 study has shown that MWA and RFA are safe and effective for BTN. The median volume reduction was 60% after a median follow-up period of 120 days, with symptomatic and cosmetic improvement ($P < 0.0001$) and no major complications. Therefore, the authors suggest that TA should be considered an alternative for patients who cannot or do not want to undergo surgery.[26]

Another recent study has shown that a single session of percutaneous, ultrasound-guided LA for BTNs provides long-term benefits and the treatment is well tolerated. Efficacy was achieved in 92% of the treated patients in 1 year. The median nodule volume significantly decreased from 16.7 mL at baseline to 5.0 mL at 1 year, a volume reduction ratio (VRR) of 68%. After 10 years of follow-up, a VRR of 59% was observed. No cases of nodule regrowth >50% were observed at 1 year.[27]

The AACE/AME/ETA Thyroid Nodule Guidelines suggest that LA may be considered for the treatment of thyroid nodules causing pressure symptoms or cosmetic issues in patients who decline surgery or are at surgical risk and does not recommend RFA in the routine management of thyroid nodules.[2]

Consensus statement

- Thermal ablation can be considered for the treatment of benign thyroid nodules causing pressure symptoms or cosmetic issues in patients who decline surgery or are at surgical risk (B/I).

What is the appropriate management for cytologically indeterminate thyroid nodules (follicular lesion of undetermined significance/atypia of undetermined significance or follicular neoplasm/suspicious for a follicular neoplasm)?

The predicted risk of malignancy for FLUS/AUS and FN or suspicious for a FN (FN/SFN) are 5%–15% and 15%–30%, respectively. The decision-making process for treatment of indeterminate nodules should be based on various parameters such as the clinical risk factors, US characteristics (elastography in addition can be considered in these cases), patient preference, and availability/feasibility of the molecular tests.[5]

FLUS/AUS category includes follicular-patterned cytology, for which a definite diagnosis of malignancy cannot be made. Repeated biopsy of nodules to check for risk of malignancy is not recommended as it does not provide any additional information, but FNA biopsy may be repeated in cases diagnosed as "atypical cells" to exclude an FN. Reports have shown that about 20% of such specimens are determined to be malignant lesions at surgical intervention.[2]

The TBSRTC 2023 third edition suggests diagnostic lobectomy or surveillance for AUS (TBSRTC Category III), diagnostic lobectomy for FN (TBSRTC Category IV), and lobectomy or near-total thyroidectomy for suspicious for malignancy (TBSRTC Category V).[13]

The AACE/AME/ETA Thyroid Nodule Guidelines recommend surgical excision of the lesion and histologic examination in most cases. Thyroid lobectomy and isthmectomy or total thyroidectomy can be considered for patients with follicular thyroid lesions based on the patient's preference and clinical situation. The guideline does not recommend intraoperative frozen section as a routine procedure. It suggests an involvement of a multidisciplinary team for follow-up without immediate diagnostic surgery in cases with favorable clinical, cytologic, and US features.[2]

The suspicious nodules (FN/SFN) include samples characterized by cytologic features that suggest malignancy but do not meet the criteria for a definite diagnosis. It may include samples with cellular features that strongly suggest malignancy. The rate of histologically confirmed malignancy in these cases is reported to be about 60%. The AACE/AME/ETA Thyroid Nodule Guidelines recommend surgery with intraoperative histologic examination or a frozen section to help guide surgical decision-making.[2]

Consensus statement

- Patients with follicular thyroid lesions having favorable clinical, US, cytologic, and immunocytochemical features should be clinically followed up without immediate diagnostic surgery. Intraoperative frozen section may not be recommended as a routine procedure for follicular lesions (A/I)
- For suspicious nodules that suggest malignancy without a definite diagnosis, surgery with intraoperative histologic examination or a frozen section can be considered (A/I)
- The initial surgical approach for patients with solitary, cytologically indeterminate nodules can be thyroid lobectomy (A/I)
- A total thyroidectomy may be recommended in indeterminate nodules that are cytologically suspicious for malignancy, positive for known mutations specific for carcinoma, sonographically suspicious, or large (>4 cm), or in patients with familial thyroid carcinoma or history of radiation exposure (A/I)
- The BSRTC 2023 system categories and recommended clinical management for cytologically indeterminate thyroid nodules are as follows (B/I):
  - Atypia of undetermined significance (AUS): Repeat FNA molecular testing, diagnostic lobectomy, or surveillance
  - Follicular neoplasm: Molecular testing, diagnostic lobectomy
  - Suspicious for malignancy: Molecular testing, lobectomy or near-total thyroidectomy.

As per the ATA, thyroid lobectomy is the recommended initial surgical approach for patients with a solitary, cytologically indeterminate nodule. A total thyroidectomy may be preferred in patients with indeterminate nodules that are cytologically suspicious for malignancy, positive for known mutations specific for carcinoma, sonographically suspicious, or large (>4 cm), or in patients with familial thyroid carcinoma or history of radiation exposure.[9]

What are the management approaches recommended for malignant thyroid nodules?

The malignant thyroid nodule category includes papillary cancer, follicular carcinoma, Hurthle cell (oncocytic) carcinoma, medullary cancer, thyroid lymphoma, anaplastic cancer, and cancer metastatic to the thyroid, and reports have suggested surgery for these patients.[5]

Active surveillance, as an alternative to surgery, is an effective approach for patients with low-risk papillary microcarcinoma (<1 cm), those with high surgical risk, short life expectancy, and concurrent surgical or medical issues that need to be addressed first.[5]

Ideal candidates for observation can be those with a STN and well-defined margins, with at least 2 mm of normal thyroid tissue surrounding it, without malignant lymph nodes, extrathyroidal extension, or suspicion for distant metastases. Such patients are suggested to be followed with high-quality sonograms and an emphasis on regular visits. For those with cytologically proven thyroid cancer, active surveillance is not recommended unless surgery is high risk.[28]

If surgery is necessary, various approaches include hemithyroidectomy (thyroid lobectomy), bilobar surgery (total thyroidectomy), or bilobar surgery with neck dissection.[28]

The AACE/AME/ETA Thyroid Nodule Guidelines recommend surgical treatment for a thyroid nodule with positive FNA biopsy results for differentiated thyroid carcinoma. It also recommends further diagnostic workup before surgery for anaplastic carcinoma, metastatic lesions, and lymphoma.[2]

As per the ATA, the initial surgical procedure should include a near-total or total thyroidectomy and gross removal of all primary tumors for patients with thyroid cancer >4 cm, or with gross extrathyroidal extension, or clinically apparent metastatic disease to nodes or distant sites.[9]

For thyroid cancer >1 cm and <4 cm without extrathyroidal extension, and without any lymph node metastases, the suggested initial procedures can be either a bilateral procedure (near-total or total thyroidectomy) or a unilateral procedure (lobectomy).[9]

The initial surgical procedure should be a thyroid lobectomy for patients with thyroid cancer <1 cm without extrathyroidal extension and lymph node metastases.[9]

Table 7 elaborates on parameters to consider for hemithyroidectomy (thyroid lobectomy) when FNA biopsy is proven malignant by different guidelines.

How are nondiagnostic thyroid nodules managed?

Nondiagnostic or unsatisfactory FNA biopsies usually result from cystic nodules that yield few or no follicular cells. These nodules can also be benign or malignant sclerotic lesions, nodules with a thick or calcified capsule, abscesses, and hypervascular or necrotic lesions.[2]

Table 7: Parameters based on different guidelines for hemithyroidectomy (thyroid lobectomy) for malignant thyroid nodules

ATA (2016)*[9]	BTA (2014)†[29]	NCCN (2016)‡[28]	AACE/ACE-AME (2016)[2]
No prior radiation No distant metastases No cervical lymph node metastases No ETE T <4 CM No familial disease Unifocal	No prior radiation No distant metastases No cervical lymph node metastases No ETE T <4 CM No familial disease <45 years Unifocal No angioinvasion	No prior radiation No distant metastases No cervical lymph node metastases No ETE T <4 CM	The extent of surgery is based on preoperative staging and the clinical setting

*If surgery is chosen for thyroid microcarcinoma, without ETE and CM, the initial surgical procedure should be lobectomy unless there are clear indications to remove the contralateral lobe, †Personalized decision-making is recommended. Also for micro-PTC, thyroid lobectomy is recommended for unifocal disease without the following identified risk factors: Nonincidental tumors, being PET positive, 6–10 mm in size, bilateral or multifocal, poorly differentiated, having extrathyroidal extension and with desmoplastic fibrosis and/or infiltrative growth pattern. ATA: American Thyroid Association, ETE: Extrathyroidal extension, CM: Cervical nodal metastases, BTA: British Thyroid Association, ‡NCCN: National Comprehensive Cancer Network, AACE: American association of clinical endocrinologist, PTC: Papillary thyroid carcinoma, PET: Positron Emission Tomography, AME/ETA: Italian association of clinical endocrinologist/European thyroid association.

Consensus statement

- For those with cytologically proven thyroid cancer, active surveillance should not recommended unless surgery is high risk (B/IIa)
- Surgical treatment should be recommended for a thyroid nodule with positive FNA biopsy results for differentiated thyroid carcinoma. Further diagnostic workup before surgery for anaplastic carcinoma, metastatic lesions, and lymphoma should be suggested (A/I)
- For patients with thyroid cancer >4 cm, or with gross extrathyroidal extension, or clinically apparent metastatic disease to nodes or distant sites, a near-total or total thyroidectomy and gross removal of all primary tumors should be recommended (A/I)
- For thyroid cancer >1 cm and <4 cm without extrathyroidal extension, and without any lymph node metastases, near-total or total thyroidectomy or a lobectomy can be suggested (A/I)
- For thyroid cancer <1 cm without extrathyroidal extension and lymph node metastases, thyroid lobectomy should be preferred as the initial procedure. (A/I)
- As per the BSRTC 2023 system, Lobectomy or near-total thyroidectomy is recommended for malignant nodules. (B/I)

Other causes for nondiagnostic results may be sampling errors or faulty biopsy techniques. Reports have shown that re-aspiration may yield satisfactory results in 50%–62% of cases, but a waiting period of at least 3 months is suggested before the procedure unless the clinical suspicion for malignancy is high.[2] Recent studies have pointed out that an earlier (in few weeks) repeat USG-guided FNAC is feasible if index of suspicion is high.

In some cases, despite initial technique and repeated biopsy, the nodules may remain nondiagnostic because of factors inherent to the lesion. In these cases, the use of US guidance and on-site cytologic evaluation may increase the rate of specimen adequacy.[2]

The ATA suggests that cytologically nondiagnostic nodule with a high suspicion sonographic pattern, growth of the nodule (>20% in two dimensions) during US surveillance, or clinical risk factors for malignancy may require surgery for histopathologic diagnosis.[9]

The AACE/AME/ETA Thyroid Nodule Guidelines suggest that CNB may offer additional information in thyroid lesions with inadequate cytologic results of FNA biopsy and that the most persistently nondiagnostic solid nodules should be surgically excised.[2]

What is the significance of intraoperative neuromonitoring during surgery?

Recurrent laryngeal nerve (RLN) is the most important structure at risk during thyroidectomy. The standard of care for protecting the RLN is identifying it through careful dissection before proceeding with the removal of the thyroid gland. Despite cautious RLN visual identification, RLN nerve injury can still occur due to anatomical variation, surgeon inexperience, and situations including large goiter, revision surgery, and invasive malignancy.[30]

Consensus statement

- FNA biopsy should be repeated with US guidance if the initial biopsy is nondiagnostic (A/I)
- Surgery should be considered for the most persistently nondiagnostic solid nodules. Surgery is also suggested for cytologically nondiagnostic nodule with a high suspicion sonographic pattern, nodule growth during US surveillance, or clinical risk factors for malignancy (A/I).

Consensus statement

- The RLN should be visually identified, and steps should be taken to preserve the external branch of the superior laryngeal nerve (EBSLN) during dissection of the superior pole of the thyroid gland (C/I)
- Intraoperative nerve monitoring can be considered to facilitate nerve identification and confirm neural conservation (C/I).

Reports have shown that only 11.3%–14% of all injured nerves are identified by visual examination.[31] Steps should be taken to avoid the nerve if the external branch of the superior laryngeal nerve (EBSLN) cannot be identified visually, which can be done by staying close to the thyroid capsule at the superior pole and by skeletonizing the superior vascular pedicle.[9]

Intraoperative nerve monitoring (IONM) is highly precise in predicting functionality and is used during thyroid surgery to identify nontransection injuries such as traction, thermal damage, compression, and clamping. Continuous-IONM (C-IONM) can help in reducing traction injury-associated neuropraxia and helps in real time to abort the causal maneuver.[31]

A recent study has shown that intraoperative stimulation and recognition of EBSLN, performed before any dissection maneuver to the superior vascular thyroid pole, lead to a much higher rate of nerve conservation.[32]

SUMMARY OF RECOMMENDATIONS

- Prevalence of thyroid nodules in the Indian population
  - The prevalence of thyroid nodules is high within the Indian population, especially in regions with iodine deficiency, mainly among women, majorly STN, with solitary nodules having a higher risk of being malignant (B/IIb).
- Causes and evaluation of thyroid nodules
  - Initial evaluation for suspected cases should include the patient's personal history of thyroid disease, malignancy, irradiation, and family history of cancers or the presence of thyroid nodules (A/I)
  - IA careful physical examination of the thyroid gland and cervical lymph nodes should be performed. It is necessary to record the location, consistency, size, tenderness, and volume of thyroid nodules (A/I)
  - IThe associated signs and symptoms should be recorded. While most nodules are asymptomatic, the absence of symptoms cannot be a criterion to rule out malignancy (A/I).
- Diagnostic methods for thyroid nodules
  - i. What are the initial laboratory tests and role of thyroid scintigraphy in the evaluation of patients with thyroid nodules?
    - Serum TSH should be measured during the initial evaluation of patients with a thyroid nodule. If TSH is suppressed, then total T3 and FT4 should be measured. If T3 and FT4 levels are also elevated, then a radionuclide scan (thyroid scintigraphy) should be performed (A/I)
    - Thyroid scintigraphy is not recommended as the initial imaging evaluation in cases with normal or elevated TSH levels (A/I).
  - ii. What is the role of ultrasonography in the detection of thyroid nodules?
    - Thyroid and neck US should be performed in all patients with clinically suspected nodular thyroid disease or incidentally detected nodules. The location, size, and features of nodules and thyroid lobes should be assessed (A/I)
    - A US-guided TI-RADS [Table 4] is suggested to be used for risk stratification of thyroid nodules (to differentiate benign from malignant lesions) and to identify which nodules warrant FNA in order to improve definite management (A/I)
    - In case of multinodularity, details of all nodules with suspicious features should be described (A/I).
  - iii. What is the role of FNA, thyroid cytology, and molecular testing in the diagnosis of thyroid nodules?

A. FNA

- Indication for FNA for thyroid nodules should be based on the combination of clinical factors, laboratory evaluation, and US risk stratification and performed under US guidance (A/I)
- The indication for FNA should be based on the following size cutoffs (A/I):
  - TR3: If nodules ≥2.5 cm (mildly suspicious)
  - TR4: If nodules ≥1.5 cm (moderately suspicious)
  - TR5: If nodules ≥1 cm (highly suspicious).
- FNA should be repeated in case of a first nondiagnostic sample, a Bethesda class III cytology, or a discrepancy between US risk score (high risk) and cytological findings (benign cytology) (A/I)
- US-guided CNB can be considered an additional procedure to FNA biopsy in selected cases (A/I).

B. Thyroid cytopathology

The Bethesda System for Reporting of Thyroid Cytopathology

(TBSRTC) 2023 recommends that every thyroid FNA report should begin with 1 of the 6 diagnostic categories. The BSRTC system categories have an implied cancer risk, which is linked to recommended clinical management.

i. Nondiagnostic: Repeat FNA with ultrasound guidance
ii. Benign: Clinical and ultrasound follow-up
iii. AUS: Repeat FNA molecular testing, diagnostic lobectomy, or surveillance
iv. FN: Molecular testing, diagnostic lobectomy
v. Suspicious for malignancy: Molecular testing, lobectomy, or near-total thyroidectomy
vi. Malignant: Lobectomy or near-total thyroidectomy.

C. Molecular testing
- Molecular testing such as analyzing cfDNA and lncRNA levels in patients with thyroid nodules can be useful molecular noninvasive diagnostic markers to help differentiate benign from malignant thyroid nodules, including in those presenting with indeterminate thyroid nodules (B/I)
- Management of thyroid nodules.

- How are benign thyroid nodules managed?
  i. Levothyroxine suppressive therapy
     - Routine TSH suppression therapy for BTNs is not necessary (A/I)
     - Levothyroxine therapy or iodine supplementation can be considered in young patients with small nodular goiter and depends on the decision by the treating physician and an endocrinologist (A/I).
  ii. Surgery for BTNs
     - Surgery for BTNs can be considered if they are growing and causing pressure or symptoms. The choice of surgery (total or hemi- or subtotal thyroidectomy) depends on the decision by the treating physician and an endocrinologist (A/I).

D. US-guided minimally invasive procedures
  i. PEI
     - PEI is safe and effective for volume reduction in thyroid cysts and thus can be considered the treatment of choice for simple cystic thyroid nodules (B/I).
  ii. TA
     - TA can be considered for the treatment of BTNs causing pressure symptoms or cosmetic issues in patients who decline surgery or are at surgical risk (B/I).

- What is the appropriate management for cytologically indeterminate thyroid nodules (FLUS/AUS or FN/SFN)?
  - Patients with follicular thyroid lesions having favorable clinical, US, cytologic, and immunocytochemical features should be clinically followed up without immediate diagnostic surgery. Intraoperative frozen section may not be recommended as a routine procedure for follicular lesions (A/I)
  - For suspicious nodules that suggest malignancy without a definite diagnosis, surgery with intraoperative histologic examination, or a frozen section can be considered (A/I).
  - The initial surgical approach for patients with solitary, cytologically indeterminate nodules can be thyroid lobectomy (A/I)
  - A total thyroidectomy may be recommended in indeterminate nodules that are cytologically suspicious for malignancy, positive for known mutations specific for carcinoma, sonographically suspicious, or large (>4 cm), or in patients with familial thyroid carcinoma or history of radiation exposure (A/I)
  - The BSRTC 2023 system categories and recommended clinical management for cytologically indeterminate thyroid nodules are as follows (B/I)
    a. AUS: Repeat FNA molecular testing, diagnostic lobectomy, or surveillance
    b. FN: Molecular testing, diagnostic lobectomy
    c. Suspicious for malignancy: Molecular testing, lobectomy or near-total thyroidectomy.
- What are the management approaches recommended for malignant thyroid nodules?
  - For those with cytologically proven thyroid cancer, active surveillance should not recommended unless surgery is high risk (B/IIa)
  - Surgical treatment should be recommended for a thyroid nodule with positive FNA biopsy results for differentiated thyroid carcinoma. Further diagnostic workup before surgery for anaplastic carcinoma, metastatic lesions, and lymphoma should be suggested (A/I)
  - For patients with thyroid cancer >4 cm, or with gross extrathyroidal extension, or clinically apparent metastatic disease to nodes or distant sites, a near-total or total thyroidectomy and gross removal of all primary tumors should be recommended (A/I)
  - For thyroid cancer >1 cm and <4 cm without extrathyroidal extension, and without any lymph node metastases, near-total or total thyroidectomy or a lobectomy can be suggested (A/I)
  - For thyroid cancer <1 cm without extrathyroidal extension and lymph node metastases, thyroid lobectomy should be preferred as the initial procedure (A/I)

    - As per the BSRTC 2023 system, lobectomy or near-total thyroidectomy is recommended for malignant nodules (B/I).
- How are nondiagnostic thyroid nodules managed?
    - FNA biopsy should be repeated with US guidance if the initial biopsy is nondiagnostic (A/I)
    - Surgery should be considered for the most persistently nondiagnostic solid nodules. Surgery is also suggested for cytologically nondiagnostic nodules with a high suspicion sonographic pattern, nodule growth during US surveillance, or clinical risk factors for malignancy (A/I).
- What is the significance of intraoperative neuromonitoring during surgery?
    - The RLN should be visually identified, and steps should be taken to preserve the EBSLN during dissection of the superior pole of the thyroid gland (C/I)
    - IONM can be considered to facilitate nerve identification and confirm neural conservation (C/I).

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REFERENCES

1. Unnikrishnan AG, Kalra S, Baruah M, Nair G, Nair V, Bantwal G, *et al.* Endocrine Society of India management guidelines for patients with thyroid nodules: A position statement. Indian J Endocrinol Metab 2011;15:2-8.
2. Gharib H, Papini E, Paschke R, Duick DS, Valcavi R, Hegedüs L, *et al.* American Association of Clinical Endocrinologists, Associazione Medici Endocrinologi, and European Thyroid Association Medical guidelines for clinical practice for the diagnosis and management of thyroid nodules: Executive summary of recommendations. Endocr Pract 2010;16:468-75.
3. Durante C, Hegedüs L, Czarniecka A, Paschke R, Russ G, Schmitt F, *et al.* 2023 European Thyroid association clinical practice guidelines for thyroid nodule management. Eur Thyroid J 2023;12:e230067.
4. Kamra HT, Agarwal R, Rana P, Kalra R, Kaur S, Duhan A, *et al.* Evaluation profile of thyroid nodule by FNAC in the rural population of Khanpur Kalan, Sonepat, Haryana. J Clin Diagn Res 2014;8:C16-8.
5. Tamhane S, Gharib H. Thyroid nodule update on diagnosis and management. Clin Diabetes Endocrinol 2016;2:17.
6. Naik D, Jebasingh F, Thomas N. Management of thyroid nodules in adults. Curr Med Issues 2018;16:42-7.
7. Kishan AM, Prasad K. Prevalence of solitary thyroid nodule and evaluation of the risk factors associated with occurrence of malignancy in a solitary nodule of thyroid. Int. Surgeon J 2018; 5: 2279-85. [doi: 10.18203/2349-2902.isj20182237].
8. Jena A, Patnayak R, Prakash J, Sachan A, Suresh V, Lakshmi AY. Malignancy in solitary thyroid nodule: A clinicoradiopathological evaluation. Indian J Endocrinol Metab 2015;19:498-503.
9. 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.
10. Biswas A, Basu K, De S, Karmakar S, De D, Sengupta M, *et al.* Correlation between thyroid imaging reporting and data system and Bethesda system of reporting of thyroid cytopathology of thyroid nodule: A single center experience. J Cytol 2020;37:193-9.
11. 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.
12. Grani G, Lamartina L, Ascoli V, Bosco D, Biffoni M, Giacomelli L, *et al.* Reducing the number of unnecessary thyroid biopsies while improving diagnostic accuracy: Toward the "Right" TIRADS. J Clin Endocrinol Metab 2019;104:95-102.
13. Ali SZ, Baloch ZW, Cochand-Priollet B, Schmitt FC, Vielh P, VanderLaan PA. The 2023 Bethesda system for reporting thyroid cytopathology. Thyroid 2023;33:1039-44.
14. De D, Dutta S, Tarafdar S, Kar SS, Das U, Basu K, *et al.* Comparison between sonographic features and fine needle aspiration cytology with histopathology in the diagnosis of solitary thyroid nodule. Indian J Endocrinol Metab 2020;24:349-54.
15. Dutta S, Tarafdar S, Mukhopadhyay P, Bhattacharyya NP, Ghosh S. Plasma cell-free DNA to differentiate malignant from benign thyroid nodules. J Clin Endocrinol Metab 2021;106:e2262-70.
16. Tarafdar S, Dutta S, Bhattacharyya NP, Mukhopadhyay P, Ghosh S. Cell free DNA integrity index to differentiate benign from malignant thyroid nodules. Endocr Abstr 2023: 90 RC2.4 [DOI: 10.1530/endoabs.90.RC2.4].
17. Dutta S, Tarafdar S, Mukhopadhyay P, Bhattacharyya NP, Ghosh S. Role of Long-Noncoding RNA (PVT1) in Determining Malignancy in Indeterminate Category of Thyroid Nodules. Late Breaking Highlighted Poster 13. Abstract Presented at the 90th Annual Meeting of the ATA.
18. Dutta S, Tarafdar S, Mukhopadhyay P, Bhattacharyya NP, Ghosh S. Circulating long non-coding RNAs as a non-invasive markers to help differentiate benign from malignancy in indeterminate thyroid nodules. Endocr Abstr 2023; 90. [doi: 10.1530/endoabs.90.OC2.5].
19. Unnikrishnan AG. Nodular diseases in the thyroid. J Assoc Physicians India 2011;59:43-5.
20. Zelmanovitz F, Genro S, Gross JL. Suppressive therapy with levothyroxine for solitary thyroid nodules: A double-blind controlled clinical study and cumulative meta-analyses. J Clin Endocrinol Metab 1998;83:3881-5.
21. Castro MR, Caraballo PJ, Morris JC. Effectiveness of thyroid hormone suppressive therapy in benign solitary thyroid nodules: A meta-analysis. J Clin Endocrinol Metab 2002;87:4154-9.
22. Madathil JP, Rajesh TR, Babu PJ. Role of thyroxine in reducing the size of benign thyroid swellings and pre-treatment thyroid stimulating hormone as a predictor of response to therapy. Int Surg J 2021;8:2707-10.
23. Guglielmi R, Pacella CM, Bianchini A, Bizzarri G, Rinaldi R, Graziano FM, *et al.* Percutaneous ethanol injection treatment in benign thyroid lesions: Role and efficacy. Thyroid 2004;14:125-31.
24. Basu N, Dutta D, Maisnam I, Basu S, Ghosh S, Chowdhury S, *et al.* Percutaneous ethanol ablation in managing predominantly cystic thyroid nodules: An Eastern India perspective. Indian J Endocrinol Metab 2014;18:662-8.
25. Bo XW, Lu F, Xu HX, Sun LP, Zhang K. Thermal ablation of benign thyroid nodules and papillary thyroid microcarcinoma. Front Oncol 2020;10:580431.
26. Gupta A, Thummar D, Yadav G, Gupta A, Yadav A. "Thyroid on Fire": Initial experience of microwave ablation for benign thyroid nodules. Arab J Intervent Radiol 2023;7:S1-41.
27. Gambelunghe G, Stefanetti E, Avenia N, De Feo P. Percutaneous

ultrasound-guided laser ablation of benign thyroid nodules: Results of 10-year follow-up in 171 patients. J Endocr Soc 2021;5:bvab081.
28. Nabhan F, Ringel MD. Thyroid nodules and cancer management guidelines: Comparisons and controversies. Endocr Relat Cancer 2017;24:R13-26.
29. Perros P, Boelaert K, Colley S, Evans C, Evans RM, Gerrard Ba G, *et al.* Guidelines for the management of thyroid cancer. Clin Endocrinol (Oxf) 2014;81 Suppl 1:1-122.
30. McManus C, Kuo JH. Intraoperative neuromonitoring: Evaluating the role of continuous IONM and IONM techniques for emerging surgical and percutaneous procedures. Front Endocrinol (Lausanne) 2022;13:808107.
31. Deshmukh A, Thomas AE, Dhar H, Velayutham P, Pantvaidya G, Pai P, *et al.* Seeing is not believing: Intraoperative nerve monitoring (IONM) in the thyroid surgery. Indian J Surg Oncol 2022;13:121-32.
32. Del Rio P, Bonati E, Loderer T, Rossini M, Cozzani F. Can we routinely identify the external branch of the superior laryngeal nerves with neural monitoring? A prospective report on 176 consecutive nerves at risk. Updates Surg 2021;73:2275-81.