

Guidelines for the Diagnosis and Management of Thyroid Nodules

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Abbreviations:

AGREE II	Appraisal of Guidelines for Research and Evaluation II
AUS	Atypia of Undetermined Significance.
CEUS	Contrast-Enhanced Ultrasound.
CNB	Core-Needle Biopsy.
CT	Computed Tomography.
EA	Ethanol Ablation.
FNA	Fine Needle Aspiration.
FNAB	Fine Needle Aspiration Biopsy.
GDG	Guideline Development Group.
GRADE	Grade of Recommendations, Assessment, Development and Evaluation.
MEA	Multiple Endocrine Anaplasia.
MEN2	Multiple Endocrine Neoplasia 2
MIT	Minimally Invasive Techniques.
MRI	Magnetic Resonance Imaging
PRO	Patient-Reported Outcome.
RAI	Radioactive Iodine.
ROM	Risk of Malignancy
RSS	Risk Stratification System.
TA	Thermal Ablation.
TBSRTC	Bethesda System for Reporting Thyroid Cytopathology.
EU-TIRADS	European Thyroid Imaging and Reporting Data System.
US	Ultrasound.
TSH	Thyroid-Stimulating Hormone.

Executive summary:

These guidelines offer evidence-based recommendations on the targeted levels of clinical practice guidelines and provide healthcare professionals with practice guidance on the surgical management of thyroid nodules and its complications.

- Initial evaluation should include age, personal and family history of MEA, Previous head or neck irradiation, physical evaluation, thyroid function testing, and neck US, (Strong recommendation).
- Neck US, including the thyroid gland and the central and lateral cervical compartments, should be performed in all patients suspected with nodular thyroid disease, (Strong recommendation).
- It is recommended for the US report to describe nodule(s) size, location, US features, and expected risk of malignancy using EU-TIRADS, (Strong recommendation).
- Doppler imaging, elasto-sonography, and CEUS may be recommended as ancillary techniques (Conditional recommendation).
- CEUS may be recommended for defining the size and boundaries of the ablated area after minimally invasive procedures, (Conditional recommendation).
- Thyroid scintigraphy is recommended when serum TSH is subnormal to diagnose functioning nodules and/or multinodularity, avoid FNA and determine eligibility for RAI as an alternative to surgery, (Strong recommendation).
- The use of CT and/or MRI in the study of thyroid nodules should be limited to the assessment of local extension or retrosternal growth of nodular goiter, (Strong recommendation).
- FNA may be recommended after clinical assessment, laboratory evaluation, and US risk stratification, in a shared decision with the patient, (Good practice statement).
- FNA is advised in:
 - EU-TIRADS 3: >20 mm, (Conditional recommendation).
- FNA is recommended in:
 - EU-TIRADS 4: >15 mm.
 - EU-TIRADS 5: >10 mm, (Strong recommendation).
- In high suspicion pattern, we recommend FNA if ≥ 10 mm, (Strong recommendation).
- In intermediate suspicion pattern, we recommend FNA if ≥ 10 mm, (Strong recommendation).
- In low suspicion pattern, we advise FNA if ≥ 15 mm, (Conditional recommendation).
- In very low suspicion pattern, we advise FNA if ≥ 20 mm (or ultrasound observation), (Conditional recommendation).
- In benign pattern, we recommend against FNA, (Strong recommendation).
- We recommend FNA regardless of lesion size when patients have a history of neck irradiation, a family history of medullary thyroid cancer or MEN2, extracapsular growth, metastatic cervical lymph nodes or Coexistent suspicious clinical findings (e.g., dysphonia), (Strong recommendation).
- Repeat FNA is recommended in case of a first non-diagnostic sample, (except in case of a solitary cyst), a Bethesda class III cytology, discrepancy between US risk score (i.e. high risk) and cytological findings (i.e. benign cytology), and significant nodule growth (an

increase $\geq 20\%$ in at least two nodule diameters with a minimum increase of 2 mm at the time of re-evaluation) of thyroid nodule(s), (Strong recommendation).

- FNA is recommended in suspicious lymph nodes, with thyroglobulin or calcitonin washout dependent on phenotype, (Strong recommendation).
- Core-needle biopsy is not recommended as a first-line tool to assess thyroid nodules after US but could be considered a second line procedure for specific conditions e.g. repeat Bethesda class III cytology and suspicion of poorly differentiated thyroid cancer, thyroid lymphoma, thyroid metastases), (Strong recommendation).
- We recommend correlation of the cytological diagnosis with clinical, ultrasound and laboratory results, (Good practice statement).
- For Bethesda I (non-diagnostic), repeat FNA is advised. If repeat FNA is still non-diagnostic, consider CNB. If still non-diagnostic, consider surgery (Conditional recommendation).
- For Bethesda II, (Benign), we are against further immediate diagnostic studies or treatment, (Strong recommendation).
- For Bethesda III, (Atypia of Undetermined Significance, (AUS)) we recommend repeating FNA and with repeat Bethesda III, consider molecular testing if available or offer surgery, (Conditional recommendation).
- For Bethesda IV, (Follicular Neoplasm), we advise molecular testing or diagnostic lobectomy, (Conditional recommendation).
- For Bethesda V, (Suspicious for malignancy), we recommend molecular testing, lobectomy, or near-total thyroidectomy, (molecular testing may help to decide whether to perform a total thyroidectomy or a thyroid lobectomy), (Strong recommendation).
- For Bethesda VI, (Malignant), we recommend lobectomy or near-total thyroidectomy, (Strong recommendation).
- We recommend multidisciplinary workup in case of advanced cancer, (Strong recommendation).
- Molecular testing is recommended in cytologically indeterminate nodules, if available, or offer surgery (Strong recommendation).
- Thyroid hormone treatment is not recommended in euthyroid individuals with nodular thyroid disease, (Strong recommendation).
- Iodine and/or selenium supplementation is not recommended unless individuals are deficient in these micronutrients, (Strong recommendation).
- RAI is recommended as an alternative to surgery and MIT in hyper-functioning solitary thyroid nodules, (Strong recommendation).
- RAI may be recommended as an alternative to surgery in benign normo-functioning multinodular goiter, (Conditional recommendation).
- EA is recommended for pure, or dominantly cystic, thyroid lesions, (Strong recommendation).
- TA is recommended for the treatment of solid benign thyroid nodules that cause local symptoms as an alternative to surgery and for cystic lesions that relapse after EA, (Strong recommendation).
- Benign cytological diagnosis is recommended before MIT. Except for EU-TIRADS 2 nodules, (Strong recommendation).
- After MIT, we recommend follow-up with clinical, biochemical and US assessments after 6 and 12 months and re-evaluating the patient after 3–5 years, (Strong recommendation).

- Surgery is recommended in the following scenarios: Symptomatic nodular thyroid disease, nodules that have been classified as benign at cytology and/or US and become symptomatic over time, calcitonin levels higher than the established cut-offs, responsive calcitonin after stimulation test in RET-mutated gene carriers, nodules with indeterminate cytology (Bethesda class III and IV) that are not suitable for active surveillance and nodules with a Bethesda class V and VI cytology, (Strong recommendation).

Introduction:

Thyroid nodules are a common clinical problem. Epidemiologic studies have shown that the prevalence of palpable thyroid nodules to be approximately 5% in women and 1% in men living in iodine-sufficient parts of the world ⁽¹⁾. In contrast, high-resolution ultrasound (US) can detect thyroid nodules in 19%–68% of randomly selected individuals, with higher frequencies in women and the elderly ⁽²⁾. Thyroid cancer occurs in 4%–15% of cases depending on age, sex, radiation exposure history, family history, and other factors ⁽³⁻⁴⁾.

Ultrasonography (US) is the primary imaging modality for evaluating thyroid nodules. The US risk stratification system (RSS) and the Thyroid Imaging Reporting and Data System (TIRADS) can help in estimating malignancy risk and guide fine-needle aspiration biopsy decisions ⁽⁵⁾.

Once FNAB has been obtained, the results can be classified according to the Bethesda System for Reporting Thyroid Cytopathology (TBSRTC). The third edition of TBSRTC, was published in 2023. Assigned single name for each of the 6 diagnostic categories: (i) nondiagnostic; (ii) benign; (iii) atypia of undetermined significance; (iv) follicular neoplasm; (v) suspicious for malignancy; and (vi) malignant, also it offers an average ROM for each category ⁽⁶⁾.

Scope and Purpose:

The scope of these guidelines is to establish a national guideline for patients with thyroid nodules as regard the need for surgery, timing, and type of surgery to achieve a best outcome as much as we can.

The main purposes of these guidelines are to minimize malpractice and poor surgical decision, to improve the quality of medical care and surgical service, to provide the best clinical practice to our patients, and finally to reduce the cost of medical service.

Target Audience:

The principle targeted audiences are the practicing surgeons, radiologists and cytopathology specialists.

Methods:

A comprehensive search for guidelines was undertaken to identify the relevant guidelines to consider for adaptation.

Inclusion/ exclusion criteria followed in the search and retrieval of guidelines to be adapted:

- Selecting only evidence-based guidelines (guideline must include a report on systematic literature searches and explicit links between individual recommendations and their supporting evidence)
- Selecting only national and/or international guidelines
- Specific range of dates for publication (using Guidelines published or updated in 2015 and later)

- Selecting peer reviewed publications only
- Selecting guidelines written in English language
- Excluding guidelines written by a single author, not on behalf of an organization to be valid and comprehensive, a guideline ideally requires multidisciplinary input
- Excluding guidelines published without references as the panel needs to know whether a thorough literature review was conducted and whether current evidence was used in the preparation of the recommendations

The following characteristics of the retrieved guidelines were summarized in:

- Developing organization/authors
- Date of publication, posting, and release
- Country/language of publication
- Date of posting and/or release
- Dates of the search used by the source guideline developers

All retrieved Guidelines were screened and appraised using AGREE II instrument (www.agreetrust.org) by at least three members. The panel decided on a cut-off point (any guideline scoring above 50% on the rigor dimension was retained). The GDG decided to adapt The American Thyroid Association Guidelines Task Force on Thyroid Nodules and Differentiated Thyroid Cancer, 2016; American college of endocrinology, and association medici endocrinologi medical guidelines for clinical practice for the diagnosis and management of thyroid nodules, 2016 and European Thyroid Association Clinical Practice Guidelines for thyroid nodule management, 2023.

Evidence assessment

According to WHO Handbook for Guidelines, we used the GRADE (Grading of Recommendations, Assessment, Development and Evaluation) approach to assess the quality of a body of evidence, develop and report recommendations. GRADE methods are used by WHO because these represent internationally agreed standards for making transparent recommendations. Detailed GRADE information is available on the following sites:

- GRADE working group: <http://www.gradeworkinggroup.org>
- GRADE online training modules: <http://cebgrade.mcmaster.ca/>
- GRADE profile software: <http://ims.cochrane.org/revman/gradepr>

Specifically, the quality of evidence was graded as ‘High’, ‘Moderate’, ‘Low’ or ‘Very low’, (table 1& 2).

The strength of the recommendation

The strength of a recommendation communicates the importance of adherence to the recommendation.

Strong recommendations

With strong recommendations, the guideline communicates the message that the desirable effects of adherence to the recommendation outweigh the undesirable effects. This means that in most situations the recommendation can be adopted as policy.

Conditional recommendations

these are made when there is greater uncertainty about the four factors above or if local adaptation has to account for a greater variety in values and preferences, or when resource use makes the intervention suitable for some, but not for other locations. This means that there is a need for substantial debate and involvement of stakeholders before this recommendation can be adopted as policy.

When not to make recommendations

When there is lack of evidence on the effectiveness of an intervention, it may be appropriate not to make a recommendation.

Recommendations:

Section 1: Initial evaluation of thyroid nodules:

- Initial evaluation should include age, personal and family history of MEA, Previous head or neck irradiation, physical evaluation, thyroid function testing, and neck US, (Strong recommendation, moderate certainty evidence ⁽⁷⁾).

Section 2: Thyroid ultrasound:

- Neck US, including the thyroid gland and the central and lateral cervical compartments, should be performed in all patients suspected with nodular thyroid disease, (Strong recommendation, moderate certainty evidence ⁽⁸⁾).
- It is recommended for the US report to describe nodule(s) size, location, US features, and expected risk of malignancy using EU-TIRADS, (Strong recommendation, moderate certainty evidence ⁽⁸⁾), (table 3).
- Doppler imaging, elasto-sonography, and CEUS may be recommended as ancillary techniques (Conditional recommendation, very low certainty evidence ⁽⁸⁾).
- CEUS may be recommended for defining the size and boundaries of the ablated area after minimally invasive procedures, (Conditional recommendation, low certainty evidence ⁽⁸⁾).

Section 3: Non-ultrasound imaging modalities:

- Thyroid scintigraphy is recommended when serum TSH is subnormal to diagnose functioning nodules and/or multinodularity, avoid FNA and determine eligibility for RAI as an alternative to surgery, (Strong recommendation, moderate certainty evidence ⁽³⁾).
- The use of CT and/or MRI in the study of thyroid nodules should be limited to the assessment of local extension or retrosternal growth of nodular goiter, (Strong recommendation, low certainty evidence ⁽³⁾).

Section 4: Thyroid biopsy:

- FNA may be recommended after clinical assessment, laboratory evaluation, and US risk stratification, in a shared decision with the patient, (Good practice statement).
- FNA is advised in:
 - EU-TIRADS 3: >20 mm, (Conditional recommendation, very low certainty evidence ⁽⁸⁾).
- FNA is recommended in:
 - EU-TIRADS 4: >15 mm.
 - EU-TIRADS 5: >10 mm, (Strong recommendation, very low certainty evidence ⁽⁸⁾).

- In high suspicion pattern, we recommend FNA if ≥ 10 mm, (Strong recommendation, moderate certainty evidence⁽³⁾), (Table 4).
- In intermediate suspicion pattern, we recommend FNA if ≥ 10 mm, (Strong recommendation, low certainty evidence⁽³⁾), (Table 4).
- In low suspicion pattern, we advise FNA if ≥ 15 mm, (Conditional recommendation, low certainty evidence⁽³⁾), (Table 4).
- In very low suspicion pattern, we advise FNA if ≥ 20 mm (or ultrasound observation), (Conditional recommendation, moderate certainty evidence⁽³⁾), (Table 4).
- In benign pattern, we recommend against FNA, (Strong recommendation, moderate certainty evidence⁽³⁾), (Table 4).
- We recommend FNA regardless of lesion size when patients have a history of neck irradiation, a family history of medullary thyroid cancer or MEN2, extracapsular growth, metastatic cervical lymph nodes or Coexistent suspicious clinical findings (e.g., dysphonia), (Strong recommendation, moderate certainty evidence⁽⁷⁾).
- Repeat FNA is recommended in case of a first non-diagnostic sample, (except in case of a solitary cyst), a Bethesda class III cytology, discrepancy between US risk score (i.e. high risk) and cytological findings (i.e. benign cytology), and significant nodule growth (an increase $\geq 20\%$ in at least two nodule diameters with a minimum increase of 2 mm at the time of re-evaluation) of thyroid nodule(s), (Strong recommendation, moderate certainty evidence⁽⁸⁾).
- FNA is recommended in suspicious lymph nodes, with thyroglobulin or calcitonin washout dependent on phenotype, (Strong recommendation, moderate certainty evidence⁽⁸⁾).
- Core-needle biopsy is not recommended as a first-line tool to assess thyroid nodules after US but could be considered a second line procedure for specific conditions e.g. repeat Bethesda class III cytology and suspicion of poorly differentiated thyroid cancer, thyroid lymphoma, thyroid metastases), (Strong recommendation, low certainty evidence⁽⁸⁾).

Section 5: Cytopathology-based management, (Based on Bethesda Categories), (Table 5):

- We recommend correlation of the cytological diagnosis with clinical, ultrasound and laboratory results, (Good practice statement).
- For Bethesda I (non-diagnostic), repeat FNA is advised. If repeat FNA is still non-diagnostic, consider CNB. If still non-diagnostic, consider surgery (Conditional recommendation, very low level of evidence,⁸).
- For Bethesda II, (Benign), we are against further immediate diagnostic studies or treatment, (Strong recommendation, high certainty evidence⁽³⁾).
- For Bethesda III, (Atypia of Undetermined Significance, (AUS)) we recommend repeating FNA and with repeat Bethesda III, consider molecular testing if available or offer surgery, (Conditional recommendation, high certainty evidence⁽⁸⁾).
- For Bethesda IV, (Follicular Neoplasm), we advise molecular testing or diagnostic lobectomy, (Conditional recommendation, low certainty evidence⁽⁸⁾).
- For Bethesda V, (Suspicious for malignancy), we recommend molecular testing, lobectomy, or near-total thyroidectomy, (molecular testing may help to decide whether to perform a total thyroidectomy or a thyroid lobectomy), (Strong recommendation, low certainty evidence⁽³⁾).
- For Bethesda VI, (Malignant), we recommend lobectomy or near-total thyroidectomy, (Strong recommendation, moderate certainty evidence⁽³⁾).

- We recommend multidisciplinary workup in case of advanced cancer, (Strong recommendation, moderate certainty evidence ⁽⁸⁾).

Section 7: Molecular diagnostics of indeterminate thyroid nodule cytology:

- Molecular testing is recommended in cytologically indeterminate nodules, if available, or offer surgery (Strong recommendation, moderate certainty evidence ⁽⁸⁾).

Section 8: Non-surgical approaches of thyroid nodules:

- Thyroid hormone treatment is not recommended in euthyroid individuals with nodular thyroid disease, (Strong recommendation, moderate certainty evidence ⁽⁸⁾).
- Iodine and/or selenium supplementation is not recommended unless individuals are deficient in these micronutrients, (Strong recommendation, low certainty evidence ⁽⁸⁾).
- RAI is recommended as an alternative to surgery and MIT in hyper-functioning solitary thyroid nodules, (Strong recommendation, moderate certainty evidence (8)).
- RAI may be recommended as an alternative to surgery in benign normo-functioning multinodular goiter, (Conditional recommendation, low certainty evidence (8)).
- EA is recommended for pure, or dominantly cystic, thyroid lesions, (Strong recommendation, moderate certainty evidence (8)).
- TA is recommended for the treatment of solid benign thyroid nodules that cause local symptoms as an alternative to surgery and for cystic lesions that relapse after EA, (Strong recommendation, low certainty evidence (8)).
- Benign cytological diagnosis is recommended before MIT. Except for EU-TIRADS 2 nodules, (Strong recommendation, low certainty evidence (8)).
- After MIT, we recommend follow-up with clinical, biochemical and US assessments after 6 and 12 months and re-evaluating the patient after 3–5 years, (Strong recommendation, low certainty evidence (8)).

Section 9: Surgical approaches of thyroid nodules:

- Surgery is recommended in the following scenarios: Symptomatic nodular thyroid disease, nodules that have been classified as benign at cytology and/or US and become symptomatic over time, calcitonin levels higher than the established cut-offs, responsive calcitonin after stimulation test in RET-mutated gene carriers, nodules with indeterminate cytology (Bethesda class III and IV) that are not suitable for active surveillance and nodules with a Bethesda class V and VI cytology, (Strong recommendation, moderate certainty evidence (8)).

Research Needs:

1. Evaluation of MITs as out-patient procedures in management of nodular goiter.
2. FNA versus CNB in assessment of thyroid nodules.
3. Molecular testing in cytologically indeterminate thyroid nodules.

Clinical Indicators of Monitoring:

1. TSH, T3, T4 testing.
2. US of the neck and TIRADS class.
3. FNA or CNB.

4. Bethesda classification.
5. Documentation of the indication of surgery in thyroid disease.
6. Documentation of the type of operation.

Updating of the Guideline:

The GDG committee for guidelines development is responsible for the continuous evaluation of evidence available about thyroid disease. The present guidelines will be updated in case of significant changes based on new evidence.

Annexes:

Table 1. Quality and Significance of the four levels of evidence in GRADE

Quality	Current definition	Previous definition
High	We are very confident that the true effect lies close to that of the estimate of the effect	Further research is very unlikely to change our confidence in the estimate of effect
Moderate	We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate
Low	Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate
Very low	We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect	Any estimate of effect is very uncertain

Table 2. Factors that determine How to upgrade or downgrade the quality of evidence

Downgrade in presence of	Upgrade in presence of
Study limitations -1 Serious limitations -2 Very serious limitations	Dose-response gradient +1 Evidence of a dose-response gradient
Consistency -1 Important inconsistency	Direction of plausible bias +1 All plausible confounders would have reduced the effect
Directness -1 Some uncertainty -2 Major uncertainty	Magnitude of the effect +1 Strong, no plausible confounders, consistent and direct evidence
Precision -1 Imprecise data	+2 Very strong, no major threats to validity and direct evidence
Reporting bias -1 High probability of reporting bias	

Table 3: EU-TIRADS categories with corresponding malignancy risks and indication of FNAC⁽⁸⁾

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

Table 4: Sonographic Patterns, Estimated Risk of Malignancy, and Fine-Needle Aspiration Guidance for Thyroid Nodules ⁽³⁾.

<i>Sonographic pattern</i>	<i>US features</i>	<i>ROM %</i>	<i>FNA size cutoff</i>
High suspicion	Solid hypoechoic nodule or solid hypoechoic component of a partially cystic nodule <i>with</i> one or more of the following features: irregular margins (infiltrative, micro lobulated), microcalcifications, taller than wide shape, rim calcifications with small extrusive soft tissue component, evidence of ETE	>70–90	Recommend FNA at ≥ 1 cm
Intermediate suspicion	Hypoechoic solid nodule with smooth margins <i>without</i> microcalcifications, ETE, or taller than wide shape	10–20	Recommend FNA at ≥ 1 cm
Low suspicion	Isoechoic or hyperechoic solid nodule, or partially cystic nodule with eccentric solid areas, <i>without</i> microcalcification, irregular margin or ETE, or taller than wide shape.	5–10	Recommend FNA at ≥ 1.5 cm
Very low suspicion	Spongiform or partially cystic nodules <i>without</i> any of the sonographic features described in low, intermediate, or high suspicion patterns	<3	Consider FNA at ≥ 2 cm Observation without FNA is also a reasonable option
Benign	Purely cystic nodules (no solid component)	<1	No biopsy

Table 5: The Bethesda system for reporting thyroid cytopathology, ROM with clinical management recommendations ⁽⁶⁾.

Diagnostic category	ROM average% (range)	Usual management
Nondiagnostic	13 (5–20)	Repeat with ultrasound guidance
Benign	4 (2–7)	Clinical and sonographic follow-up
Atypia of Undetermined Significance	22 (12–30)	Repeat FNA, molecular testing, diagnostic lobectomy, or surveillance
Follicular neoplasm	30 (23–34)	Molecular testing, diagnostic lobectomy
Suspicious for Malignancy	74 (67–83)	Molecular testing, lobectomy, or near-total thyroidectomy
Malignant	97 (97–100)	Lobectomy or near-total thyroidectomy

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