

Diagnostic and Therapeutic Approach to Thyroid Nodules

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ABSTRACT

Thyroid nodules are highly prevalent in the adult population, particularly when detected by high-resolution ultrasound, yet only a minority represent clinically significant malignancy. Contemporary management has shifted from routine biopsy or surgery toward a risk-adapted strategy aimed at identifying nodules with meaningful malignant potential, autonomous function, compressive symptoms, or cosmetic impact while avoiding overdiagnosis and overtreatment. Initial evaluation should include clinical history, physical examination, serum thyroid-stimulating hormone, and high-quality neck ultrasonography. Radionuclide scintigraphy is indicated when thyroid-stimulating hormone is suppressed to identify hyperfunctioning nodules, which are rarely malignant and are usually managed according to thyroid functional status. Ultrasound-based risk stratification systems guide the need for fine-needle aspiration according to sonographic pattern and size thresholds. Fine-needle aspiration with Bethesda cytology remains the cornerstone of preoperative diagnosis, although indeterminate cytology continues to represent a major challenge. Molecular testing can refine malignancy risk in selected indeterminate nodules but remains limited by cost, access, local cancer prevalence, and variable impact on patient-centered outcomes. Most benign asymptomatic nodules require observation rather than intervention. Surgery is reserved for malignant, suspicious, symptomatic, compressive, or selected indeterminate nodules. Minimally invasive treatments, including ethanol ablation and thermal ablation, are increasingly used for selected benign symptomatic nodules. This review summarizes the diagnostic pathway, cytologic interpretation, therapeutic options, follow-up strategies, and emerging technologies in thyroid nodule management.

KEYWORDS: thyroid nodule; thyroid ultrasound; fine-needle aspiration; Bethesda system; thyroid cancer; molecular testing; radiofrequency ablation; ethanol ablation; active surveillance.

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INTRODUCTION

Thyroid nodules are among the most common findings in endocrine practice. Their prevalence depends on the method of detection: palpation identifies only a minority, whereas high-resolution ultrasound can detect nodules in a large proportion of adults. Despite their frequency, most thyroid nodules are benign and clinically indolent.

The main clinical challenge is to distinguish nodules that require intervention from those that can be safely observed. Historically, many nodules underwent routine biopsy or diagnostic surgery, contributing to unnecessary procedures,

patient anxiety, and healthcare costs. Modern management emphasizes risk stratification using serum thyroid-stimulating hormone, ultrasound features, selective fine-needle aspiration, standardized cytology, and individualized follow-up.

The current approach is not simply to detect all nodules, but to identify clinically relevant disease: thyroid cancer with meaningful progression risk, autonomous nodules causing thyrotoxicosis, and benign nodules producing compressive or cosmetic symptoms [1–3].

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METHODS

This narrative review was developed from the uploaded literature synthesis on diagnostic and therapeutic management of thyroid nodules. The included evidence consisted of major society guidelines, narrative reviews, consensus statements, studies on ultrasound risk stratification, cytology, molecular testing, minimally invasive treatment, artificial intelligence, and active surveillance.

References are numbered according to their first appearance in the manuscript.

Initial Clinical Evaluation

Evaluation begins with a focused history and physical examination. Important historical features include:

Childhood or adolescent neck irradiation

Family history of thyroid cancer or thyroid cancer syndromes

Rapid nodule growth

Hoarseness or voice change

Dysphagia or dyspnea

Neck pressure or compressive symptoms

Prior thyroid disease

History of autoimmune thyroiditis

Symptoms of hyperthyroidism or hypothyroidism

Physical examination should assess thyroid size, nodule consistency, fixation, cervical lymphadenopathy, tracheal deviation, and signs of thyroid dysfunction. A hard fixed nodule, vocal cord dysfunction, or suspicious lymph nodes

increases concern for malignancy and should prompt specialist evaluation.

Although history and examination are important, they cannot reliably distinguish benign from malignant nodules. Therefore, biochemical and imaging evaluation are essential. Serum Thyroid-Stimulating Hormone

Serum thyroid-stimulating hormone is the initial laboratory test in most patients with a thyroid nodule. It determines whether the nodule should proceed directly to ultrasound-based risk stratification or whether functional imaging is needed.

When thyroid-stimulating hormone is normal or elevated, radionuclide scintigraphy is usually not required, and ultrasound becomes the main diagnostic test.

When thyroid-stimulating hormone is suppressed, radionuclide scintigraphy should be performed to determine whether the nodule is hyperfunctioning, isofunctioning, or nonfunctioning [4–6].

Hyperfunctioning nodules are rarely malignant and typically do not require routine fine-needle aspiration unless there are highly suspicious features or discordant clinical findings. Their management is directed toward control of thyrotoxicosis and may include radioiodine, surgery, antithyroid medication, or minimally invasive ablation in selected settings.



Figure 1 Product of total thyroidectomy with diagnosis of Multinodular Goiter with thyroid nodule tirads 4 Bethesda 5

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Neck Ultrasound

High-quality ultrasound is the central imaging modality in thyroid nodule evaluation. It characterizes nodule size, composition, echogenicity, margins, shape, calcifications, vascularity, extrathyroidal extension, and cervical lymph nodes.

Suspicious ultrasound features include:

Solid composition

Marked hypoechogenicity

Irregular or infiltrative margins

Microcalcifications

Taller-than-wide shape

Extrathyroidal extension

Suspicious cervical lymph nodes

Low-risk features include:

Pure cystic composition

Spongiform appearance

Isoechoic or hyperechoic solid pattern without suspicious features

Smooth margins

Comet-tail artifacts in colloid nodules

Ultrasound should also evaluate the central and lateral neck lymph node compartments when malignancy is suspected. Suspicious nodes may show microcalcifications, cystic change, peripheral vascularity, rounded shape, or loss of fatty hilum.

Ultrasound Risk Stratification Systems

Several ultrasound risk stratification systems are used internationally, including:

American Thyroid Association sonographic patterns

ACR TI-RADS

EU-TIRADS

Korean TI-RADS

British Thyroid Association U classification

Although these systems differ in scoring structure and biopsy thresholds, they share the same principle: nodules with more suspicious features and larger size are selected for fine-needle aspiration, while very low-risk nodules are followed or ignored.

The purpose is to reduce unnecessary biopsy of benign nodules without missing clinically significant cancers. Selective biopsy is now standard practice because many nodules detected incidentally have minimal clinical significance [2,7,8].

Fine-Needle Aspiration Biopsy

Fine-needle aspiration is the primary diagnostic procedure for thyroid nodules that meet ultrasound and size criteria. It is usually performed under ultrasound guidance, which improves accuracy and reduces nondiagnostic sampling.

Fine-needle aspiration is generally indicated when:

The nodule has suspicious ultrasound features and meets size criteria.

There are suspicious cervical lymph nodes.

There is growth or new suspicious imaging change during follow-up.

Clinical risk factors raise pretest probability.

The result will alter management.

Fine-needle aspiration should not be performed on every detected nodule. Biopsy of very small or very low-risk nodules may increase overdiagnosis, unnecessary surgery, and patient anxiety without improving outcomes.

Bethesda Cytology System

The Bethesda System standardizes reporting of thyroid cytology and links categories to malignancy risk and management.

Common categories include:

Nondiagnostic or unsatisfactory

Benign

Atypia of undetermined significance or follicular lesion of undetermined significance

Follicular neoplasm or suspicious for follicular neoplasm

Suspicious for malignancy

Malignant

Benign cytology is highly reassuring when the ultrasound pattern is concordant. Malignant or suspicious cytology usually leads to surgery or, in selected very low-risk cancers, active surveillance.

Indeterminate categories, particularly Bethesda III and IV, represent the main diagnostic challenge because cytology cannot reliably distinguish benign follicular-patterned lesions from malignancy.

Indeterminate Thyroid Nodules

Indeterminate cytology occurs in a substantial minority of biopsied nodules. Management depends on:

Bethesda category

Ultrasound risk pattern

Nodule size

Patient age and comorbidities

Family and radiation history

Molecular testing availability

Patient preference

Local cancer prevalence

Surgical risk

Options include repeat fine-needle aspiration, molecular testing, core needle biopsy in selected cases, diagnostic lobectomy, or surveillance.

A suspicious ultrasound pattern despite benign or indeterminate cytology should prompt reassessment, repeat sampling, or surgical evaluation. Conversely, an indeterminate nodule with low-risk ultrasound features and reassuring molecular testing may be observed.

Molecular Testing

Molecular testing can improve preoperative risk stratification in indeterminate nodules. These tests may function as “rule-out” tools, “rule-in” tools, or combined classifiers depending on the platform.

Potential benefits include:

Reducing unnecessary diagnostic surgery

Improving selection for lobectomy versus total thyroidectomy

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Identifying mutations associated with higher malignancy risk
Supporting surveillance decisions in low-risk cases

However, molecular testing has important limitations. Its predictive value depends on local disease prevalence, cytology category, test platform, sample quality, and the definition of clinically meaningful cancer. Cost and access also vary widely across health systems.

Current evidence supports molecular testing as an additional tool for selected indeterminate nodules, not as a replacement for clinical judgment, ultrasound interpretation, cytology, or patient preference [9–11].

Core Needle Biopsy

Core needle biopsy is not routinely required for most thyroid nodules but may be considered when fine-needle aspiration is repeatedly nondiagnostic or when specific diagnoses are suspected.

Potential indications include:

Repeated nondiagnostic cytology

Discordant suspicious ultrasound and benign cytology

Suspected lymphoma

Suspected anaplastic thyroid cancer

Suspected metastatic disease

Fibrosing thyroiditis

Need for histologic architecture or immunohistochemistry

Core needle biopsy should be performed by experienced operators because complications, although uncommon, may include bleeding, pain, or injury to adjacent structures.

Management of Benign Thyroid Nodules

Most benign thyroid nodules do not require active treatment. Observation is appropriate when the nodule is asymptomatic, cytologically benign, and sonographically low risk.

Follow-up is usually based on ultrasound risk pattern rather than size alone. Repeated ultrasound may be performed at longer intervals for stable low-risk nodules. Routine repeated biopsy is not necessary unless the nodule develops suspicious features or shows clinically meaningful growth.

Treatment may be considered when benign nodules cause:

Dysphagia

Dyspnea

Neck pressure

Globus sensation

Cosmetic deformity

Recurrent cystic enlargement

Hyperfunction

Patient distress after appropriate counseling

Surgery

Surgery remains the definitive treatment for malignant, suspicious, compressive, or selected indeterminate nodules.

Indications

Surgery may be indicated for:

Malignant cytology

Suspicious cytology

Indeterminate cytology with high-risk features

Symptomatic compressive nodules

Large nodules causing structural symptoms

Hyperfunctioning nodules unsuitable for radioiodine or ablation

Patient preference after counseling

Concern for aggressive disease

Suspicious lymph nodes requiring compartment-oriented management

Extent of Surgery

The extent of surgery depends on cancer risk, tumor size, multifocality, extrathyroidal extension, nodal disease, contralateral nodules, patient preference, and surgeon expertise.

Options include:

Diagnostic lobectomy

Therapeutic lobectomy

Total thyroidectomy

Completion thyroidectomy

Central or lateral neck dissection when indicated

Lobectomy may be adequate for many low-risk cancers and indeterminate nodules, reducing the likelihood of lifelong hypoparathyroidism and bilateral recurrent laryngeal nerve risk. Total thyroidectomy may be required for larger, bilateral, high-risk, or advanced disease.

Potential complications include recurrent laryngeal nerve injury, hypoparathyroidism, bleeding, infection, hypothyroidism, and need for lifelong thyroid hormone replacement.

Active Surveillance for Low-Risk Thyroid Cancer

Active surveillance is now an accepted option for selected patients with small low-risk papillary thyroid carcinomas, especially papillary microcarcinomas.

Ideal candidates include patients with:

Small intrathyroidal tumor

No clinical nodal metastasis

No extrathyroidal extension

No aggressive cytology or histology

Tumor not adjacent to the recurrent laryngeal nerve or trachea

Reliable follow-up

Preference to avoid immediate surgery

Active surveillance requires structured ultrasound follow-up and clear criteria for delayed surgery, such as tumor growth, nodal disease, or change in risk features.

This approach reduces overtreatment but requires patient understanding, psychological readiness, and experienced multidisciplinary care [12].

Radioiodine Therapy

Radioiodine is used mainly for autonomous hyperfunctioning nodules and toxic multinodular goiter. It reduces hormone production and may shrink nodule volume over time.

Advantages include:

Nonoperative treatment

Effective control of hyperthyroidism

Useful in older or higher-risk surgical patients

Limitations include:

Delayed effect

Risk of hypothyroidism

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Contraindication in pregnancy and lactation

Less immediate relief of compressive symptoms

Radiation safety precautions

Radioiodine is not used as primary treatment for benign nonfunctioning nodules unless there is a specific functional indication.

Ethanol Ablation

Ethanol ablation is particularly useful for recurrent benign cystic or predominantly cystic thyroid nodules.

It involves ultrasound-guided aspiration of cyst contents followed by instillation of ethanol to induce sclerosis of the cyst wall. It is relatively low cost, technically simple, and effective for recurrent cystic lesions.

Limitations include pain, leakage of ethanol, transient voice change, need for repeated treatment, and lower efficacy in solid nodules.

Ethanol ablation is generally preferred over thermal ablation for recurrent cystic nodules because of its simplicity and efficacy [13,14].

Thermal Ablation

Thermal ablation includes:

Radiofrequency ablation

Laser ablation

Microwave ablation

High-intensity focused ultrasound

Radiofrequency ablation is the most widely used technique for benign solid or predominantly solid nodules causing symptoms or cosmetic concerns.

Advantages

Minimally invasive

No surgical scar

Usually outpatient

Preserves thyroid tissue

Low risk of hypothyroidism

Reduces nodule volume and symptoms

Limitations

Operator dependent

Requires benign confirmation before treatment

May require repeat sessions

Regrowth can occur

Not suitable for all nodule locations

Limited role in high-risk malignancy

Thermal ablation should generally be reserved for nodules with confirmed benignity, usually requiring at least one or two benign cytology results depending on guideline context and sonographic risk [13,15].

Management of Hyperfunctioning Nodules

A suppressed thyroid-stimulating hormone should prompt scintigraphy. Hyperfunctioning nodules are usually benign but may cause subclinical or overt hyperthyroidism.

Treatment options include:

Radioiodine

Surgery

Radiofrequency ablation in selected cases

Antithyroid medication as temporary or selected long-term therapy

Treatment is especially important in older patients and those at risk for atrial fibrillation, osteoporosis, or cardiovascular complications.

Fine-needle aspiration is not routinely required for hyperfunctioning nodules unless ultrasound or clinical features are discordant and suspicious.

Incidental Thyroid Nodules

Thyroid nodules are often found incidentally on CT, MRI, carotid ultrasound, PET/CT, or other imaging.

The need for thyroid ultrasound depends on:

Age

Nodule size

Suspicious imaging findings

PET avidity

Lymphadenopathy

Invasion or local mass effect

Patient comorbidities and life expectancy

PET-avid thyroid nodules carry a higher malignancy risk than many other incidental nodules and usually warrant dedicated ultrasound and possible biopsy if appropriate.

In older patients with major comorbidity or limited life expectancy, aggressive evaluation of small incidental nodules may not provide benefit.

Artificial Intelligence

Artificial intelligence is increasingly studied for thyroid ultrasound interpretation, cytology assistance, risk prediction, and clinical decision support.

Potential applications include:

Automated ultrasound feature detection

Malignancy risk prediction

Standardization of TI-RADS classification

Reduction of unnecessary biopsy

Cytology image interpretation

Integration of ultrasound, clinical, and molecular data

Early studies show promising diagnostic performance.

However, artificial intelligence tools are not yet ready to replace expert clinical judgment. Key limitations include dataset bias, variable external validation, workflow integration, medicolegal issues, interpretability, and lack of prospective outcome data [16–18].

Follow-Up Strategy

Follow-up should be individualized according to initial risk.

For benign low-risk nodules, follow-up ultrasound may be performed at longer intervals or discontinued when stability is established. For higher-risk ultrasound patterns with benign cytology, closer follow-up or repeat biopsy may be warranted. Clinically meaningful growth is usually defined by significant increase in at least two dimensions or volume, but growth alone is not always a sign of malignancy. New suspicious ultrasound features are more concerning than size increase alone.

Follow-up should also assess:

Symptoms

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Cosmetic concerns

Thyroid function

Lymph nodes

Patient anxiety

Need for repeat biopsy or treatment

Proposed Diagnostic and Therapeutic Algorithm

Identify the nodule clinically or incidentally.

Obtain serum TSH.

If TSH is suppressed, perform radionuclide scintigraphy.

If the nodule is hyperfunctioning, treat according to thyroid function and symptoms.

If TSH is normal or elevated, perform high-quality neck ultrasound.

Classify ultrasound risk using a validated system.

Perform FNA only if ultrasound pattern and size meet criteria.

Report cytology using the Bethesda system.

Observe benign low-risk nodules.

Repeat FNA, consider molecular testing, or consider diagnostic surgery for indeterminate nodules.

Treat malignant or suspicious nodules with surgery or active surveillance when appropriate.

Use ethanol ablation for recurrent benign cystic nodules.

Use thermal ablation for selected symptomatic benign solid nodules.

Individualize follow-up according to risk, symptoms, and patient preference.

DISCUSSION

The strongest consensus in thyroid nodule care is that management should be selective and risk stratified. Most nodules are benign and do not require biopsy or treatment. Therefore, indiscriminate ultrasound screening, routine biopsy of small low-risk nodules, and surgery for all detected lesions should be avoided.

Serum thyroid-stimulating hormone, ultrasound risk stratification, and selective fine-needle aspiration form the

diagnostic core. Cytology remains highly useful, but indeterminate categories remain challenging. Molecular testing can reduce diagnostic surgery in selected cases, but its value depends on local context and should not be applied automatically.

Therapeutic management has also become less invasive. Observation is appropriate for most benign asymptomatic nodules. Active surveillance is reasonable for selected low-risk papillary microcarcinomas. Ethanol and thermal ablation provide effective nonsurgical options for selected benign symptomatic nodules.

The future of thyroid nodule management will likely include better integration of ultrasound, cytology, molecular profiling, artificial intelligence, patient preference, and cost-effectiveness. However, the central principle will remain the same: identify clinically important disease while minimizing harm from overdiagnosis and overtreatment.

CONCLUSION

Thyroid nodules should be managed through a personalized, risk-adapted pathway. Initial evaluation requires serum thyroid-stimulating hormone and high-quality neck ultrasound. Fine-needle aspiration should be reserved for nodules that meet sonographic and size-based criteria. Bethesda cytology guides most decisions, while molecular testing may help selected indeterminate nodules. Most benign asymptomatic nodules require observation only. Surgery is indicated for malignant, suspicious, symptomatic, or selected indeterminate nodules. Radioiodine is useful for autonomous hyperfunctioning nodules, ethanol ablation for recurrent benign cystic nodules, and thermal ablation for selected benign symptomatic solid nodules. Optimal care balances cancer detection, symptom relief, functional status, cost, and avoidance of unnecessary intervention.

Table 1. Diagnostic and Therapeutic Approach to Thyroid Nodules

Clinical scenario	Recommended approach	Main purpose	Important limitation
Newly detected thyroid nodule	History, examination, serum TSH, neck ultrasound	Determine functional and structural risk	Clinical examination alone cannot determine malignancy
Suppressed TSH	Radionuclide scintigraphy	Identify hyperfunctioning nodule	Does not replace ultrasound assessment when suspicious features exist
Normal or elevated TSH	Ultrasound risk stratification	Decide whether FNA is needed	Operator-dependent interpretation
Low-risk cystic or spongiform nodule	Observation or limited follow-up	Avoid unnecessary biopsy	May require treatment if symptomatic
Suspicious ultrasound pattern	FNA if size threshold is met	Cytologic diagnosis	Small low-risk cancers may still be observed
Benign cytology	Surveillance according to ultrasound risk	Avoid overtreatment	Repeat evaluation if discordant or evolving features appear
Nondiagnostic cytology	Repeat ultrasound-guided FNA or core biopsy in selected cases	Obtain adequate tissue	Repeated nondiagnostic results may require surgery

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Indeterminate cytology	Repeat FNA, molecular testing, surveillance, or diagnostic lobectomy	Refine malignancy risk	Molecular testing depends on cost, access, and local prevalence
Malignant or suspicious cytology	Surgery or active surveillance in selected low-risk cancers	Definitive treatment or controlled observation	Surgery carries recurrent nerve and parathyroid risks
Recurrent benign cystic nodule	Ethanol ablation	Cyst volume reduction	May require repeat treatment
Symptomatic benign solid nodule	Radiofrequency or other thermal ablation	Reduce volume and symptoms without surgery	Regrowth and operator dependence
Autonomous hyperfunctioning nodule	Radioiodine, surgery, or selected ablation	Treat thyrotoxicosis	FNA is usually not needed unless discordant suspicious features exist

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