

REVIEW ARTICLE

Overdiagnosis of low-risk thyroid cancer: Autopsy insights and guideline-driven management

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Abstract

The global rise in thyroid cancer incidence over recent decades is largely attributed to increased detection of papillary thyroid microcarcinomas (PTMCs; ≤ 1 cm) from widespread ultrasonography and ultrasonography-guided fine-needle aspiration. Meanwhile, the associated mortality has remained stable or declined, suggesting significant overdiagnosis. Autopsy studies consistently report incidental differentiated thyroid cancer in 4–36% of individuals, with prevalence up to 36% in thorough whole-gland examinations, indicating that many small papillary carcinomas are indolent and clinically insignificant during a patient's lifetime. This review synthesizes evidence from autopsy findings, epidemiological trends, and long-term observational studies to evaluate how screening and diagnostic intensity contribute to rising thyroid cancer diagnoses. We compare recommendations from the 2015 and 2025 American Thyroid Association guidelines, the 2022 National Health Commission of the People's Republic of China guidelines, and the Bethesda System for Reporting Thyroid Cytopathology, with attention to active surveillance, de-escalated surgery, reduced radioactive iodine use, and minimally invasive techniques (e.g., radiofrequency ablation) for appropriately selected low-risk PTMCs. Remaining areas of debate, including the management of lymph node metastases, the interpretation of recurrence risk, the utility and limitations of thyroglobulin monitoring in conservative management settings, and the enhanced accuracy of molecular testing, were also discussed. The analysis supports the value of refined risk stratification and patient-centered decision-making to reduce overtreatment and its associated morbidity while maintaining vigilance for the minority of cases with more aggressive behavior.

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1. Introduction

The incidence of thyroid cancer, particularly papillary thyroid carcinoma (PTC), has surged over the past four decades, with papillary thyroid microcarcinomas (PTMCs; ≤ 1 cm in size) increasing from 25.0% of diagnoses in 1988 to 47.5% in 2016.^{1,2} This “epidemic” coincides with the widespread adoption of high-resolution ultrasonography

and ultrasonography-guided fine-needle aspiration (FNA), yet thyroid cancer mortality remains stable, suggesting overdiagnosis of clinically insignificant lesions.^{1,3-5} Autopsy studies report incidental differentiated thyroid cancer (iDTC) in 4–36% of cases, indicating that many thyroid cancers are subclinical and do not progress to symptomatic disease.⁶⁻⁸ Overdiagnosis and overtreatment strain healthcare systems, expose patients to surgical risks (e.g., hypoparathyroidism and vocal cord paralysis), and necessitate lifelong thyroid hormone replacement, impacting quality of life.

The shift toward conservative management, including active surveillance for low-risk PTMCs, reflects growing recognition of their indolent nature. However, challenges remain, including clinician adherence to guidelines, patient anxiety, and controversies over lymph node management. This review aims to:

- (i) Summarize the prevalence of iDTC and thyroid nodules in autopsy studies.
- (ii) Evaluate the role of screening in driving overdiagnosis.
- (iii) Compare guideline recommendations for thyroid nodule and cancer management, focusing on PTMCs.
- (iv) Discuss the Bethesda System for Reporting Thyroid Cytopathology's role in risk stratification and reclassification of low-risk lesions.
- (v) Address controversies in lymph node metastasis (LNM) management and recurrence risks.
- (vi) Explore emerging strategies, such as innovations in the fields of radiofrequency ablation (RFA) and thyroglobulin (Tg) monitoring.
- (vii) Propose strategies to reduce overtreatment while ensuring timely intervention for aggressive cases.

This movement toward de-escalation is further reinforced by contemporary patient-centered evidence: In a large multicenter cohort of low-risk PTMC patients, 24.2% of those who underwent thyroidectomy experienced heightened decision regret—compared with only 3.4% under active surveillance—driven predominantly by post-operative scar-related and psychological quality-of-life impairment.⁹ By integrating evidence from the 2015 and 2025 American Thyroid Association (ATA) guidelines,^{10,11} 2022 National Health Commission of the People's Republic of China (NHCPRC) guidelines,¹² the Bethesda System,¹³ and recent studies, this review seeks to inform clinical practice and policy in an era of overdiagnosis.

2. Prevalence of thyroid cancer in autopsy studies

Autopsy studies are pivotal for understanding the natural history of thyroid cancer, revealing a high prevalence of

incidental findings that contextualize the diagnostic epidemic. Several terms describe thyroid carcinomas discovered without prior clinical suspicion. Historically, occult PTC referred to non-palpable papillary carcinomas (typically <1 cm) that were clinically silent and most commonly discovered at autopsy. The term was later also applied to tumors presenting with clinically apparent LNMs, despite a microscopic or ultrasonographically overlooked primary lesion in the thyroid. Latent PTC denotes asymptomatic cases undetected during life, typically found at autopsy. Occult carcinoma of the thyroid (OCT) applies more broadly to any impalpable thyroid carcinoma (<1 cm), including incidental or autopsy findings. The contemporary umbrella term iDTC encompasses well-differentiated carcinomas (primarily papillary, sometimes follicular) identified unexpectedly through autopsy, imaging, or surgery for unrelated conditions. In this review, historical terminology is preserved for original studies, while iDTC is used consistently to discuss broader patterns and implications.

A landmark 1985 study by Finnish pathologists systematically examined thyroid glands, finding papillary thyroid cancer in 35.6% of specimens, leading to the conclusion that low-risk thyroid cancers are a “normal finding.”⁶ The authors noted that occult papillary carcinoma is usually very small, most often under 1 mm, generally circumscribed, and lacking aggressive features, indicating that incidentally found occult papillary carcinoma, particularly those under 5 mm, should not be treated. A 2016 meta-analysis of 35 studies spanning six decades reported iDTC prevalence of 4.1% (95% confidence interval [CI]: 3.0–5.4%) in partial thyroid examinations and 11.2% (95% CI: 6.7–16.1%) in whole thyroid examinations.⁷ The ATA's review of this meta-analysis emphasized that prevalence depends on examination thoroughness, with no significant increase since 1970, indicating that the rise in diagnosed cases reflects enhanced detection rather than true incidence.⁸ Thyroid nodules are highly prevalent, with autopsy studies reporting rates of 13–60%, palpation detecting only 0.5–6.5%, and ultrasonography identifying 13.4–46%, as indicated by Stanić *et al.*¹⁴ These prevalence rates for thyroid cancer and nodules are summarized in [Table 1](#). While approximately 5% of these nodules may be or become malignant, the majority are benign, leading to concerns of overdiagnosis. Stanić *et al.*¹⁴ further emphasized that thyroid ultrasonography should not be performed without a clear clinical indication determined by a thyroid specialist. The high prevalence of iDTC and nodules underscores the indolent nature of most thyroid abnormalities, which rarely progress to clinical disease. For example, the Finnish study's findings suggest that many individuals harbor subclinical cancers that remain asymptomatic throughout life.⁶

Table 1. Prevalence of incidental thyroid cancer and nodules in autopsy studies

Study	Cancer type	Prevalence (%)	Examination type	Population (sample size)	Notes
Harach <i>et al.</i> ⁶	OPC	35.6	Whole thyroid	Finnish (<i>n</i> =101)	Single study, systematic, low-risk OPC considered “normal finding”
Furuya-Kanamori <i>et al.</i> ⁷	iDTC	4.1 (partial, 95% CI: 3.0–5.4) 11.2 (whole, 95% CI: 6.7–16.1)	Partial/Whole	Global (35 studies)	Meta-analysis, prevalence stable since 1970, depends on examination thoroughness
Stančić <i>et al.</i> ¹⁴	Nodules	13–60 (nodules) ~5% of nodules are potentially malignant	Partial/Whole	Global (multiple studies)	Review, not all nodules are histologically confirmed; the malignancy rate is estimated

Abbreviations: iDTC: Incidental differentiated thyroid cancer; OPC: Occult papillary carcinoma.

Methodological variability in autopsy studies significantly influences reported prevalence estimates of thyroid cancer. Key contributing factors include section thicknesses (varying between 4 μ m and 4 mm), population characteristics (such as age, sex, and history of radiation exposure), and the extent of examination conducted (partial vs. whole gland).^{6,7,15} Notably, whole-gland examinations, as performed in the Finnish study, yield substantially higher prevalence rates than partial gland assessments, emphasizing the critical need for standardized and comprehensive protocols to ensure consistent and comparable results. For example, a Spanish autopsy study found a 5.28% prevalence of OCT with partial gland examination but 22% with whole-gland examination.¹⁶ Moreover, regional variations, including iodine intake levels in populations such as those in Finland, may also contribute to differences in prevalence, although this association remains speculative and not conclusively demonstrated.^{17,18}

A meta-analysis comparing 1,355 clinically evident PTMCs with 989 latent PTCs from 15 autopsy studies further elucidated their differences.¹⁵ The study found that latent PTCs were typically smaller (<1–3 mm) and more often multifocal compared to PTMCs (30.5% vs. 24.7%, $p<0.001$). Interestingly, latent PTCs showed a balanced male-to-female ratio (1:1), whereas PTMCs had a marked female predominance (1:10.9) and higher rates of cervical LNM (33.4% vs. 10.0%). Although the observed LNM rate was lower in latent PTCs, this difference was not statistically significant, potentially because lymph nodes were not examined systematically in autopsy studies, suggesting these metastases are often subclinical. Similarly, a meta-analysis of 29 autopsy studies found that adverse histological features, including minimal extrathyroidal extension (24.5%), multifocality (28.2%), vascular invasion (16%), and LNMs (11%), are common in occult differentiated thyroid cancers (DTCs) but, when associated with small tumors, do not indicate aggressive disease, suggesting that current guidelines may need revision.¹⁹ Another meta-analysis found a stable

subclinical PTC prevalence (12.9% for whole-gland and 4.6% for partial-gland examinations) across all age groups, suggesting that increased clinical diagnoses in middle age reflect diagnostic scrutiny rather than a higher subclinical reservoir.²⁰ Adding further evidence from earlier studies, an autopsy series of 1,020 thyroid glands demonstrated a 6.2% prevalence of OCT, almost all of which were papillary and measured 0.5–10.5 mm in diameter. Multicentricity was frequent (46%), while 14% showed regional LNMs that did not manifest as clinical disease, supporting their indolent nature. These tumors showed no sex or age predilection, and their presence did not indicate progression to clinically apparent thyroid cancer.²¹ Furthermore, small-volume LNMs in PTC are associated with a low recurrence risk (3–8% for fewer than five nodes), supporting the notion that such metastases in autopsy-detected PTCs are likely clinically insignificant. However, the risk increases with a higher nodal burden (7–21% for more than five nodes).²²

These findings suggest that latent PTCs and PTMCs may represent distinct categories, with the former appearing less aggressive and less likely to require treatment. However, it is currently not possible to reliably distinguish between them in clinical practice, underlining the risk of conflating the two in decision-making. This limitation highlights the need for more standardized and comprehensive autopsy studies to refine our understanding of subclinical thyroid cancers and to inform evidence-based guidelines. At the same time, the high prevalence of incidental cancers detected at autopsy raises doubts about the clinical significance of many such lesions, strengthening arguments against routine screening in asymptomatic individuals and reinforcing the importance of risk stratification to minimize overtreatment and its potential harms.

3. Overdiagnosis and the role of screening

The thyroid cancer “epidemic” is primarily a diagnostic phenomenon driven by increased detection of PTMCs through widespread ultrasonography and FNA in high-resource countries.^{1,3–5} Over the past 30 years,

the age-standardized prevalence of thyroid cancer has increased, whereas the age-standardized mortality and disability-adjusted life year rates have decreased,^{23,24} as reflected in the data from the global burden of disease (GBD) project.²⁵ The age-standardized incidence rate and age-standardized mortality rates per 100,000 population,

as reported by the GBD, are presented in [Figure 1](#). These data demonstrate a clear global decline in mortality alongside a sustained rise in incidence; notably, the trend in incidence is beginning to plateau or reverse in high sociodemographic index countries, largely attributed to the adoption of evidence-based clinical guidelines that

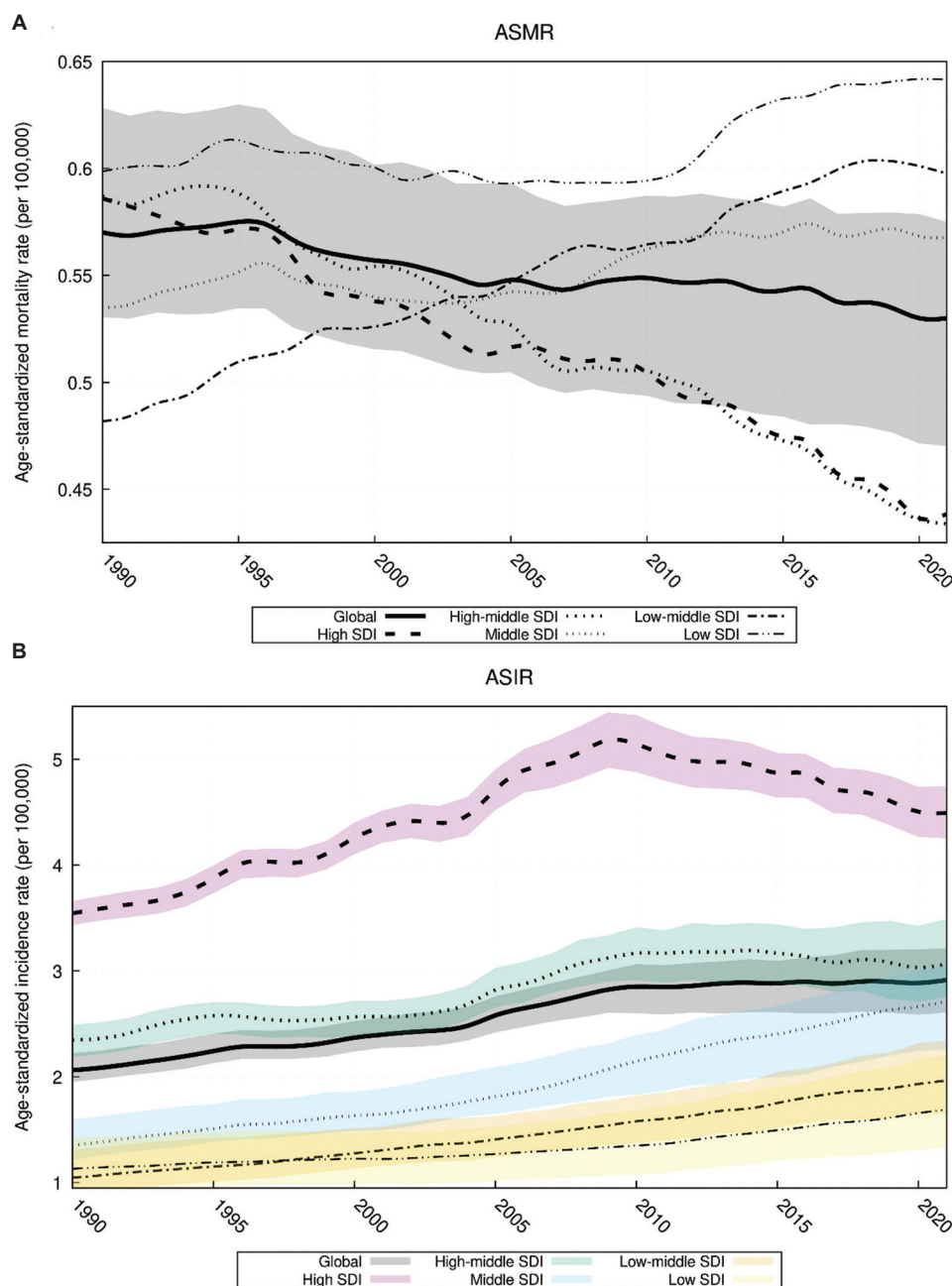


Figure 1. (A) Age-standardized mortality rates (ASMR) and (B) age-standardized incidence rates (ASIR) per 100,000 population, extracted from the global burden of disease project database, are shown for global and Sociodemographic index-based trends from 1990 to 2021. Uncertainty is represented as confidence bands—shaded areas illustrating the range of uncertainty around the estimates. Confidence bands are displayed for all ASIR trends, whereas for ASMR, a single confidence band is shown only for the global trend to avoid overlap and enhance visibility. Images created by the author with Gnuplot (version 5.4).

promote more selective and judicious use of diagnostic procedures. Other epidemiological investigations, such as the one by Jin *et al.*,²⁶ published in the Journal of Global Health, have reached the same conclusion, reporting rising incidence largely driven by overdiagnosis while mortality continues to decline. A major data source used in their study and many similar international analyses is the Global Cancer Observatory (GLOBOCAN 2022), maintained by the International Agency for Research on Cancer under the World Health Organization (WHO).

In South Korea, a nationwide study found that aggressive screening was associated with a more than 7-fold increase in diagnoses, rising from 6.3/100,000 population in 1999 to 47.5/100,000 population in 2009, along with a significant 20.1-fold increase in small tumors (<10 mm) and an 8.1-fold increase in regional stage tumors, with no corresponding increase in mortality.⁴ Similarly, China's rising incidence correlates with expanded ultrasonography use, particularly in urban areas, where screening programs have become routine despite limited evidence of benefit.³ The influence of regulatory capture—where screening policies favor industry interests—has also been highlighted in some reports.⁵ Worldwide, the pattern of overdiagnosis of indolent papillary microcarcinomas is well documented. In Italy, overdiagnosis accounted for 75% of female and 63% of male cases diagnosed between 1998 and 2012, with more than threefold regional variation in incidence.²⁷ In 2020, age-standardized incidence rates varied by more than 15-fold among women across 185 countries, while mortality rates remained uniformly low ($\leq 0.5/100,000$ women and $\leq 0.3/100,000$ men in nearly all settings).²⁸ From 1998 to 2012, the rise in thyroid cancer incidence observed globally was almost entirely attributable to papillary carcinoma, which showed consistent increases across diverse regions, including Europe, North America, Latin America, Oceania, and Asia, whereas other histological subtypes showed stable or decreasing trends.²⁹ Despite the rising incidence, long-term international mortality trends have generally continued to decline or remain stable.³⁰ In the United States, this pattern is exemplified by a sharp decline in incidence since 2014, particularly for papillary tumors ≤ 1 cm (annual percent change: -5.83%), localized disease, and small/indolent lesions, while rates for tumors >2 cm have plateaued amid stable mortality at approximately $0.5/100,000$, indicating reduced overdiagnosis rather than a true decrease in aggressive disease.³¹ Consistent with this, autopsy studies showing a stable prevalence of subclinical PTCs (4.1–35.6%) across the lifespan suggest that this diagnostic epidemic reflects detection of indolent tumors rather than a true increase in disease, especially in the context of early-onset thyroid cancer.^{6,7,20}

The 2017 United States Preventive Services Task Force issued a grade D recommendation against routine screening for thyroid cancer in asymptomatic adults. This decision was made after determining that, although the incidence of thyroid cancer diagnoses has significantly increased in recent years, there has been no corresponding rise in mortality. Furthermore, the evidence indicates that screening and treatment provide only a minimal benefit. Conversely, there is moderate certainty of at least moderate harms, mainly due to unnecessary diagnoses and treatments, which can include serious surgical complications and the effects of overtreatment. As a result, the conclusion is that screening offers a negative net benefit for the general asymptomatic adult population.³² The NHCPRC guidelines¹² also advise against routine screening in low-risk populations, recommending it exclusively for high-risk groups. These high-risk individuals include those with a history of neck radiation or exposure to radioactive contamination during childhood, as well as those with a family history of thyroid cancer or thyroid cancer syndromes. In addition, individuals presenting with positive ^{18}F -fluorodeoxyglucose (^{18}F -FDG) lesions, elevated serum calcitonin levels, or abnormal cervical lymph nodes are also considered high-risk and may warrant ultrasound-guided FNA biopsy if ≤ 1 cm thyroid nodules are incidentally found.

These recommendations reflect a growing consensus that overscreening leads to the detection of subclinical cancers that would not have caused harm, consistent with autopsy findings of prevalent but indolent PTCs. South Korea's experience, where screening programs led to a surge in PTMC diagnoses without survival benefits, underscores the need for targeted approaches.⁴ Overdiagnosis also has economic implications, with increased healthcare costs from diagnostic procedures, surgeries, and lifelong hormone therapy. Addressing this requires policy changes, such as clinician training on enhanced risk stratification and the diagnosis, risk/benefit assessment, treatment decisions, response assessment (DATA) framework per the 2025 ATA guidelines, which promote active surveillance for low-risk DTC, particularly cT1aN0M0 (clinical tumors ≤ 1 cm in greatest dimension, confined to the thyroid, no lymph node or distant metastases) PTMCs. Emerging evidence also supports consideration of active surveillance for select cT1bN0M0 tumors (clinical tumors >1 cm but ≤ 2 cm, also confined to the thyroid, no lymph node or distant metastases). The guidelines emphasize less aggressive management compared to the 2015 recommendations through reduced radioactive iodine (RAI) use and less frequent follow-up for low-risk cases. Regulatory oversight to limit unnecessary ultrasonography

use aligns with recommendations to restrict screening to high-risk groups.^{10–12}

4. Guideline recommendations for thyroid nodule management

The 2015 and 2025 ATA guidelines, alongside the 2022 NHCPRC guidelines, provide evidence-based frameworks for managing thyroid nodules and DTC, emphasizing risk stratification, shared decision-making, and reducing overtreatment to optimize patient outcomes.^{10–12} The 2015 ATA guidelines comprehensively address both thyroid nodules and DTC in a single document, covering evaluation (e.g., ultrasonography and FNA) and management (e.g., active surveillance, surgery, RAI, and percutaneous ablation).¹⁰ The 2025 ATA guidelines separate these into two documents: One for DTC management (published in *Thyroid*, August 2025¹¹) and another for thyroid nodule evaluation, unpublished as of September 2025. The NHCPRC guidelines align with ATA recommendations, emphasizing multidisciplinary consultation for optimal prognosis.¹²

4.1. Screening

Routine screening is not recommended for asymptomatic individuals without specific risk factors. The 2015 ATA guidelines advise against routine ultrasound screening for familial follicular cell-derived DTC due to insufficient evidence of reduced morbidity or mortality (Recommendation 1) and recommend initial evaluation of a thyroid nodule through serum thyroid-stimulating hormone (TSH) measurement, with a ¹²³I radionuclide scan if TSH is subnormal, but not if normal or elevated (Recommendation 2). Serum Tg and calcitonin measurements are not routine (Recommendations 3 and 4). In this respect, the 2025 ATA guidelines suggest ultrasound screening for first-degree relatives of familial non-medullary thyroid cancer with ≥3 affected members or two affected with concerning features (e.g., young age at diagnosis) (Recommendation 4). Similarly, the NHCPRC guidelines recommend screening high-risk patients (e.g., history of radiation exposure or a family history of DTC/medullary thyroid carcinoma [MTC]/multiple endocrine neoplasia type II/Cowden syndrome) with multidisciplinary consultation (Section 2.1 in NGCPRC guidelines).

4.2. Diagnostic evaluation

The 2015 ATA guidelines recommend ultrasonography-guided FNA for nodules ≥1 cm in greatest dimension with high or intermediate suspicion sonographic patterns, nodules ≥1.5 cm with low suspicion, or nodules ≥2 cm with very low suspicion (e.g., spongiform). FNA is not

required for nodules <1 cm in greatest dimension or purely cystic, although clinical high-risk factors (e.g., history of radiation exposure or family history of thyroid cancer) may justify FNA at lower size cutoffs (see Section A10, Recommendation 8 in 2015 ATA guidelines, along with management guidance in Recommendations 10C, 21, and 35C). Cytology should follow the Bethesda System (Recommendation 9), with repeat FNA for non-diagnostic results (Recommendation 10).

The NHCPRC guidelines recommend FNA for nodules >1 cm in greatest dimension with more than one malignant ultrasound sign (e.g., microcalcification, irregular margin, and taller-than-wide); not for nodules ≤1 cm unless abnormal lymph nodes, radiation history, family history, positive lesions on ¹⁸F-FDG positron emission tomography (PET)/computed tomography (CT), or elevated calcitonin (Section 2.4.1 in NHCPRC guidelines). The guidelines also exclude FNA for hot nodules with autonomous uptake on thyroid nuclide imaging and purely cystic nodules.

Although the 2025 ATA guidelines lack updated nodule-specific recommendations as of September 2025, they strongly recommend pre-operative neck ultrasonography to assess cervical lymph nodes and extrathyroidal extension in all patients undergoing surgery for malignancy (Recommendation 7A). Ultrasonography-guided FNA should be performed on suspicious lymph nodes ≥8–10 mm in the smallest diameter if it will impact management (Recommendation 7B). In addition, FNA with Tg washout may be considered in select cases, albeit difficult to interpret in patients with an intact thyroid and supported by low certainty evidence (Recommendation 7C).

4.3. Molecular testing

Molecular testing—such as B-Raf proto-oncogene, serine/threonine kinase (BRAF) and the seven-gene panel (including *BRAF*, *RAS*, *RET/PTC*, and *PAX8/PPARG*)—is endorsed by the 2015 ATA guidelines for indeterminate cytology categories (atypia of undetermined significance [AUS]/follicular lesion of undetermined significance [FLUS], follicular neoplasm [FN]/suspicious for FN [SFN], and suspicious for papillary carcinoma) to guide management. Testing should be performed in Clinical Laboratory Improvement Amendments/College of American Pathologists-certified laboratories or those with equivalent international accreditation, with appropriate patient counseling on the benefits and limitations (Recommendations 13–17). However, the guidelines emphasize that the value of molecular testing in determining post-operative RAI use has not been demonstrated; therefore, no recommendation can be

made for its use in this context due to insufficient evidence (Recommendation 52).

Recent advancements in next-generation sequencing (NGS) have further refined these tools, with panels such as ThyroSeq v3 (a DNA/RNA-based NGS assay interrogating 112 genes for mutations, fusions, copy number alterations, insertion–deletion, and gene expression) and *Afirma* gene sequencing classifier (GSC; an RNA-based NGS classifier analyzing ~10,000 genes) demonstrating superior performance over prior generations (e.g., ThyroSeq v2, *Afirma* gene expression classifier [GEC]) in reducing diagnostic uncertainty for Bethesda III/IV nodules (Section 5.1).^{33–35} These tests excel in “rule-out” strategies, with high negative predictive values (NPVs; >94%) enabling non-operative management for benign/negative results while maintaining low false-negative rates (<6% over 3-year follow-up).^{33,34} A 2023 prospective randomized trial ($n = 372$ indeterminate nodules) conducted at the University of California, Los Angeles, directly compared ThyroSeq v3 and *Afirma* GSC, reporting similar diagnostic accuracies.³³ The sensitivity was greater than 95% for both tests, with a specificity of 80% for *Afirma* GSC compared to 85% for ThyroSeq v3 ($p=0.33$). The positive predictive value (PPV) was 57% for GSC versus 64% for v3 (95% CIs: 45–69% and 51–77%, respectively), and the NPV was 100% for GSC compared to 99% for v3, assuming non-surgical benign results. In surgically confirmed cases, the NPV for ThyroSeq v3 was 92% (95% CI: 76–100%), with one false negative. The trial compellingly demonstrated a reduction of approximately 50% in the occurrence of diagnostic surgeries based on benign or negative test results.

In addition, a 2022 meta-analysis pooled data from studies involving 472 thyroid nodules tested with *Afirma* GSC, reporting a sensitivity of 96.6% (95% CI: 89.7–98.9%) and a specificity of 52.9% (95% CI: 23.4–80.5%). The PPV was 63% (95% CI: 51–74%), and the NPV was 96% (95% CI: 94–98%).³⁴ Similarly, pooled data from ThyroSeq v3 studies including 530 nodules showed a sensitivity of 95.1% (95% CI: 91.1–97.4%), a specificity of 49.6% (95% CI: 29.3–70.1%), a PPV of 70% (95% CI: 55–83%), and an NPV of 92% (95% CI: 86–97%).

Moreover, a 2021 systematic review and meta-analysis reported that ThyroSeq v3 and *Afirma* GSC demonstrate superior overall diagnostic accuracy compared to earlier molecular tests, with ThyroSeq v3 showing the highest area under the curve (0.95) and improved rule-out capabilities, while corroborating preliminary positive results for microRNA-based panels.³⁵ However, ThyroSeq v2 remains the most effective molecular test for ruling in malignancy. In a related context, recent subset analyses focusing on

nodules with Hürthle cell cytology revealed that *Afirma* GSC demonstrated a significantly higher benign call rate of 84% compared to 56% for ThyroSeq v3, enabling more patients to avoid surgery without compromising malignancy detection.³⁶

These NGS panels thus enhance risk stratification by identifying indolent lesions (e.g., non-invasive follicular thyroid neoplasm with papillary-like nuclear features [NIFTP] and *RAS*-mutated) suitable for active surveillance, while flagging high-risk alterations (e.g., *BRAF* V600E and *TERT* promoter mutations) for surgical intervention.^{11,34} In relation to DTC, the 2025 ATA guidelines do not routinely recommend pre-operative genomic evaluation of confirmed DTC but suggest using known genomic profiles (e.g., *BRAF*, *RAS*, and *TERT*) with clinical data to inform surgical extent (Recommendation 10). Post-operative molecular profiling may refine risk stratification if data are available (Recommendation 28B), while germline testing is advised for syndromic features (e.g., Cowden syndrome and cribriform-morular carcinoma) (Recommendations 2 and 5). Finally, the NHCPRC guidelines note molecular testing (e.g., *BRAF*, *RAS*, *RET/PTC*) as informative for indeterminate nodules but do not recommend it routinely, following ATA for indeterminate cases (Section 2.3.2 in NHCPRC guidelines).

4.4. Active surveillance

The 2015 ATA guidelines acknowledge that active surveillance may be considered as an alternative to immediate surgery in selected patients with very-low-risk PTMCs (≤ 1 cm, intrathyroidal, cN0M0, away from critical structures) (Section A14, Recommendation 12 in 2015 ATA guidelines). The guidelines also highlight, in Section D3, that additional research is needed to define optimal surveillance strategies, including ultrasound frequency, Tg monitoring, TSH targets, and criteria for intervention. Similarly, the NHCPRC guidelines endorse active surveillance for low-risk PTMCs (single lesion <1 cm, central thyroid location, no regional LNM), with re-evaluation every 6 months and surgery if progression occurs (e.g., 2–3 mm growth or new suspicious nodes) (Section 4.1.2 in NHCPRC guidelines).

Notably, the 2025 ATA guidelines expand active surveillance to cT1aN0M0 PTMCs, with emerging evidence supporting consideration in select cT1bN0M0 tumors (≤ 2 cm), using the DATA framework for shared decision-making (Recommendation 11A). Surveillance involves ultrasonography monitoring (Recommendation 12), with surgery indicated for growth ≥ 3 mm, lymph node/distant metastases, extrathyroidal extension, posterior growth, or patient preference (Recommendation 14).

Routine Tg/anti-Tg antibodies (TgAb) measurement is not recommended (Recommendation 13).

4.5. Surgical indications

For patients with cT1N0M0 PTC, the 2015 ATA guidelines suggest that a lobectomy is typically adequate if surgery is chosen, unless a risk assessment indicates the need for a total thyroidectomy. For tumors measuring 1–4 cm (classified as cT1–T2, where cT1 refers to clinically apparent tumors ≤ 2 cm and cT2 refers to tumors > 2 cm and ≤ 4 cm; both confined to the thyroid) and with cN0 (indicating no nodal metastasis), either a lobectomy or total thyroidectomy may be considered based on clinical and patient-specific factors. A total thyroidectomy is recommended for tumors exceeding 4 cm, classified as cT3–T4 (tumors extending beyond the thyroid into adjacent structures), as well as for cN1 (clinical evidence of nodal metastasis) and cM1 (presence of distant metastasis) (Recommendation 35). Prophylactic central neck dissection is considered a weak recommendation with low-quality evidence for T3/T4 (T3: Tumor > 4 cm limited to thyroid or tumor of any size with gross extrathyroidal extension involving strap muscles; T4: Tumor with gross extrathyroidal extension invading nearby structures) and cN1b (metastases to lateral neck lymph nodes) (Recommendation 36).

Correspondingly, the NHCPRC guidelines recommend thyroid lobectomy for T1 and T2 DTC confined to one lobe, reflecting their usual unifocal nature. Total thyroidectomy is advised for T3 and T4 tumors, multifocal lesions, lymph node or distant metastases, family history of DTC, and childhood ionizing radiation exposure (Section 4.1.2 in NHCPRC guidelines). For tumors in the isthmus, extended isthmus resection may be considered for small lesions, while larger tumors or those with nodal metastases generally require total thyroidectomy. Central and lateral neck lymph node dissection recommendations depend on clinical nodal status and risk factors, with careful attention to nerve preservation and parathyroid gland management during central compartment dissection.

The 2025 ATA guidelines recommend lobectomy for cT1N0M0 (≤ 2 cm), prefer lobectomy for cT2N0M0 (2–4 cm) unless RAI or enhanced follow-up is needed, and strongly recommend total thyroidectomy for cT3–T4, cN1, and cM1 (Recommendation 15). High-volume surgeons (> 25 –50 thyroidectomies/year) are preferred (Recommendation 6), and prophylactic central neck dissection is not advised in most patients with small, non-invasive cT1–T2 cN0 PTC and in most follicular thyroid cancers (Recommendation 19).

4.6. Ablation

The 2015 ATA guidelines do not routinely recommend RAI remnant ablation for low-risk DTC or unifocal/multifocal

PTMCs without adverse features. However, if RAI is used, a low administered activity around 30 mCi is typically recommended. For patients with higher-risk disease, RAI may be used in adjuvant therapy to address potential microscopic residual disease, in which case, administered activities greater than remnant ablation doses, typically up to 150 mCi, are recommended (Recommendations 51, 55, and 56). Percutaneous ethanol injection is advised for recurrent cystic nodules (Recommendation 28), and RFA or cryoablation are valid minimally invasive options for treating distant metastases (Recommendation 93).

By contrast, the NHCPRC guidelines do not mention percutaneous ablation, focusing instead on surgery or surveillance. RAI remnant ablation is not routinely recommended for low-risk DTC or unifocal PTMC, but may be considered for follow-up (~ 30 mCi, or 100 mCi if a large remnant remains). Adjuvant therapy is indicated for high-risk and selected intermediate-risk patients, typically at 100–150 mCi. RAI therapy for persistent, recurrent, or metastatic disease is usually given at 150–200 mCi (Section 5.3 in NHCPRC guidelines).

The 2025 ATA guidelines do not recommend RAI routinely for low-risk DTC, suggest considering RAI for low-intermediate/intermediate-high risk, and highly recommend it for high-risk or metastatic DTC (Recommendation 32). Percutaneous ablation (RFA, ethanol) is introduced as an alternative to surgery or surveillance for cT1aN0M0 PTMCs (Recommendation 11B) and for recurrent/residual disease if reoperation is high-risk (Recommendation 52).

4.7. Post-operative management

Post-operative ultrasonography is recommended at 6–12 months following surgery, with subsequent evaluations conducted periodically based on risk factors and Tg status, according to the 2015 ATA guidelines (Recommendation 65). Serum Tg and TgAb are measured every 6–12 months, with more frequent testing for high-risk patients. It is strongly recommended, with high-quality evidence, that Tg and TgAb levels be monitored longitudinally in patients using consistent assay methods within the same laboratory to ensure accuracy and comparability of results over time (Recommendation 62). TSH suppression targets are < 0.1 mU/L for high-risk, 0.1–0.5 mU/L for intermediate-risk, and 0.5–2 mU/L for low-risk patients (Recommendation 59).

In alignment with this, the NHCPRC guidelines recommend monitoring serum Tg and TgAb beginning 6 months post-RAI, with reassessment at 12 months and thereafter every 6–12 months. For intermediate- and high-risk patients, more frequent dynamic Tg monitoring over

3 years is advised. Neck ultrasonography is recommended at 3 months post-surgery for high-risk patients and at 6 months for low- or intermediate-risk patients. If suspicious lymph nodes are identified, the interval between scans should be shortened, and further evaluation with FNA, including FNA-Tg washout measurement, or biopsy should be performed as indicated (Section 9.2 in NHCPRC guidelines). The target TSH suppression levels are risk-adapted, with TSH <0.1 mU/L for high-risk, 0.1–0.5 mU/L for intermediate-risk, and 0.5–2.0 mU/L for low-risk patients (Section 5.4 in NHCPRC guidelines). Thyroid function should be re-evaluated 4–6 weeks after thyroxine dose adjustments, with follow-up intervals extended if stable. These recommendations aim to detect recurrent or metastatic disease early, evaluate treatment response, optimize TSH suppression, and monitor for potential treatment-related complications (Section 9.2 in NHCPRC guidelines). For MTC, calcitonin and carcinoembryonic antigen monitoring is recommended, with calcitonin ≥ 150 pg/mL or doubling time indicating progression (Section 2.3.2 in NHCPRC guidelines).

The measurement of Tg is recommended 6–12 weeks post-thyroidectomy, along with ultrasound at 6–12 months, as outlined in the 2025 ATA guidelines (Recommendation 30). The timing and frequency of these evaluations should be adjusted based on risk factors and patient response (Recommendation 31). TSH suppression decisions should be individualized, particularly for high-risk patients who may benefit more from maintaining TSH levels in the subnormal range, while long-term TSH suppression is not recommended for low- or intermediate-risk patients without evidence of biochemical or structural recurrence (Recommendations 45 and 46). In addition, low-risk patients with sustained excellent response may discontinue routine ultrasonography after 5–8 years and Tg/TgAb after 10–15 years (Recommendation 48).

4.8. Patient-oriented guidance

The 2018 ATA patient brochure regarding PTMCs³⁷ delineates that low-risk PTMCs—characterized as solitary lesions measuring <1 cm in diameter, centrally situated within the thyroid and distanced from critical anatomical structures such as the trachea and recurrent laryngeal nerve, and devoid of regional LNMs as determined by imaging or clinical assessment—exhibit an exceedingly low mortality risk of <1 in 1,000. The brochure underscores that both surgical excision and active surveillance are viable management strategies, thereby promoting a patient-centered approach to decision-making in these low-risk scenarios. This perspective is consistent with the 2025 ATA guidelines, which emphasize the importance of shared decision-making frameworks, such as the

DATA framework. These guidelines advocate for active surveillance in cases of low-risk DTC, particularly microcarcinomas, to mitigate the risks of overtreatment while taking into account patient preferences. A summary of management recommendations for thyroid nodules and DTCs from the 2015 and 2025 ATA guidelines, as well as the NHCPRC Chinese guidelines, is presented in [Table 2](#).

Despite current guidelines, surveys show that 67% of clinicians perform FNA on suspicious thyroid nodules smaller than 1 cm based solely on sonographic features, highlighting a significant gap between recommended practice and real-world clinical behavior.^{38,39} This overutilization contributes to overdiagnosis and overtreatment, as many subcentimeter nodules are benign or indolent. Clinician education, multidisciplinary tumor boards, and decision-support tools may improve adherence to guidelines, reducing unnecessary interventions while ensuring timely management of high-risk cases.

5. The Bethesda System and cytopathology

The Bethesda System for Reporting Thyroid Cytopathology standardizes FNA interpretation and provides implied risks of malignancy to guide clinical management. Although the third edition was published in 2023 with refined terminology, updated risk-of-malignancy estimates, and subdivision of the AUS category, the majority of current clinical outcome data and guideline recommendations—including the 2025 ATA guidelines for DTCs—remain anchored to the widely implemented second edition (2017).¹³ This review, therefore, primarily references the second-edition categories and risks ([Table 3](#)) while noting that the third-edition refinements, discussed in Section 5.4, do not fundamentally alter management algorithms for most nodules and tend to further reduce overtreatment of indeterminate lesions by lowering certain post-test malignancy risks. The six diagnostic categories of the second edition are non-diagnostic, benign, AUS/FLUS, FN/SFN, suspicious for malignancy (SFM), and Malignant.

5.1. Diagnostic categories

The categories include:

- Bethesda I: Non-diagnostic (3–34% frequency in FNA interpretation, 5–10% malignancy risk): Often due to insufficient cellularity or cyst fluid, requiring repeat FNA with ultrasound guidance.
- Bethesda II: Benign (60–70% of all thyroid FNAs, 0–3% malignancy risk): Managed with clinical follow-up unless symptomatic.
- Bethesda III: AUS/FLUS (1–22% frequency, 10–30% malignancy risk): Characterized by the presence of few cells with mild nuclear atypia or more extensive but very mild nuclear atypia. Molecular testing for the

Table 2. Comparison of the ATA and NHCPRC guidelines for thyroid nodule and DTC management

Aspect	ATA (2015) ¹⁰	ATA (2025) ¹¹	NHCPRC (2022) ¹²
Screening	No routine US screening for familial follicular cell-derived DTC; insufficient evidence for reduced morbidity/mortality (Rec. 1). Initial evaluation: Serum TSH; if subnormal, ¹²³ I scan; if normal/elevated, no radionuclide scan (Rec. 2). No routine Tg (Rec. 3) or calcitonin (Rec. 4).	No routine US screening; considered for first-degree relatives of FNMTC (≥3 affected or 2 with concerning features, e.g., young age) (Rec. 4). Tg/TgAb not routine for surveillance (Rec. 13).	No routine US screening for the general population; recommended for high-risk patients (prior radiation, family history of DTC/MTC/MEN-II/Cowden) with multidisciplinary consultation (Sec. 2.1).
Diagnostic evaluation (FNA)	FNA for nodules: ≥1 cm (high/intermediate suspicion), ≥1.5 cm (low suspicion), ≥2 cm (very low suspicion, e.g., spongiform); not required for <1 cm or purely cystic unless clinical risk factors (e.g., radiation exposure, family history) (Sec. A10; Rec. 8). Bethesda System for cytology (Rec. 9). Repeat FNA for non-diagnostic results (Rec. 10).	No updated nodule-specific guidelines as of September 2025. Assumes nodular FNA continuity with 2015 and confirmed PTC. FNA of suspicious lymph nodes (8–10 mm) if results would impact management (Rec. 7B). FNA-Tg washout in select pre-operative cases (challenging interpretation with intact thyroid; low-certainty evidence) (Rec. 7C).	FNA for nodules >1 cm with ≥1 malignant US sign (e.g., microcalcification, irregular margin, taller-than-wide); not for ≤1 cm unless abnormal lymph nodes, history of neck radiation exposure/childhood radiation contamination, family history of thyroid cancer/syndrome, positive ¹⁸ F-FDG PET/CT, or elevated calcitonin; excludes hot nodules with autonomous uptake or purely cystic nodules (Sec. 2.4.1 and Sec. 2.6.1, Bethesda System).
Molecular testing	Molecular testing for AUS/FLUS (Rec. 15), FN/SFN (Rec. 16), SUSP (Rec. 17) in CLIA/CAP laboratories; counsel on benefits/limitations (Recs. 13 and 14). <i>BRAF</i> /7-gene panel (<i>BRAF</i> , <i>RAS</i> , <i>RET/PTC</i> , <i>PAX8/PPARG</i>) for SUSP if alters surgery (Rec. 17). Not routine for post-operative RAI assessment (Rec. 52).	Not routine pre-surgery in confirm DTC; if known, genomic profile (e.g., <i>BRAF</i> , <i>RAS</i> , <i>TERT</i>) informs surgical extent with clinical data (Rec. 10). Post-operative molecular profiling is not routine but refines risk if obtained (Rec. 28B). Germline testing for syndromic features (e.g., Cowden syndrome, cribriform-morular carcinoma) (Recs. 2 and 5).	Molecular testing (e.g., <i>BRAF</i> , <i>RAS</i> , <i>RET/PTC</i>) may be informative for indeterminate nodules; not routine, follows the ATA approach for indeterminate (Sec. 2.3.2).
Active surveillance	Supported for low-risk PTMCs (≤1 cm, intrathyroidal, cN0M0, not near critical structures) with active surveillance as an alternative to surgery in properly selected patients (Sec. A14, Rec. 12, and Section. D3).	Offered for cT1aN0M0 PTCs with the DATA framework for shared decision-making (Rec. 11A). Emerging evidence also supports consideration for select cT1bN0M0 tumors. US monitoring (Rec. 12); surgery if growth ≥3 mm, metastases, extrathyroidal extension, posterior growth, or patient preference (Rec. 14). No routine Tg/TgAb (Rec. 13).	Low-risk PTMC (single <1 cm, central location, no lymph node metastases); US re-evaluation every 6 months; surgery for 2–3 mm growth or new suspicious nodes (Sec. 4.1.2).
Surgical indications	Lobectomy for cT1N0M0 (≤2 cm) unless risk factors (e.g., radiation, family history); lobectomy or total thyroidectomy for 1–4 cm (cT1–T2, cN0); total thyroidectomy for >4 cm, cT3–T4 (gross extrathyroidal extension), cN1, or cM1 (Rec. 35). Prophylactic central neck dissection for T3/T4 or cN1b (Rec. 36).	Lobectomy for cT1N0M0 (≤2 cm); lobectomy preferred for cT2N0M0 (2–4 cm) unless RAI or enhanced follow-up needed; total thyroidectomy for cT3–T4, cN1, or cM1 (Rec. 15). High-volume surgeons (>25–50/year) preferred (Rec. 6). No prophylactic central neck dissection for cT1–T2, cN0 (Rec. 19).	Lobectomy for T1/T2 confined to one lobe; total thyroidectomy for T3/T4, multifocal lesions, lymph node/distant metastases, family history, or childhood radiation; central dissection for cN1a, lateral for cN1b (Sec. 4.1.2).
Ablation	RAI remnant ablation is not routine for low-risk or unifocal/multifocal PTMCs without adverse features (30 mCi; Recs. 51 and 55). Adjuvant RAI for intermediate/high-risk (up to 150 mCi; Recs. 51 and 56). PEI for recurrent cystic nodules (Rec. 28); RFA/cryoablation for distant metastases (Rec. 93).	RAI is not routine for low-risk; considered for low-intermediate/intermediate-high risk; routine for high-risk or distant metastases (Rec. 32). Percutaneous ablation (RFA, ethanol) for cT1aN0M0 PTCs as an alternative to surgery/surveillance (Rec. 11B); ethanol/RFA for recurrent/residual disease if high-risk reoperation (Rec. 52).	RAI remnant ablation not routine for low-risk/unifocal PTMC (30 mCi favored); adjuvant for intermediate/high-risk (100–150 mCi); therapy for metastatic disease (150–200 mCi); no percutaneous ablation, prefers surgery/surveillance (Sec. 5.3).

(Cont'd...)

Table 2. (Continued)

Aspect	ATA (2015) ¹⁰	ATA (2025) ¹¹	NHCPRC (2022) ¹²
Post-operative management	Post-operative US at 6–12 months, then per risk/Tg status (Rec. 65). Tg and TgAb every 6–12 months, more frequent for high-risk (Rec. 62). TSH suppression: <0.1 mU/L (high-risk), 0.1–0.5 mU/L (intermediate), 0.5–2 mU/L (low-risk) (Rec. 59).	US at 6–12 months, then per risk/response (Rec. 31). Tg/TgAb 6–12 weeks post-thyroidectomy (Rec. 30); TSH suppression individualized; not suggested for low/intermediate-risk without recurrence (Recs. 45 and 46). Low-risk with excellent response may stop US after 5–8 years, Tg/TgAb after 10–15 years (Rec. 48).	Tg/TgAb every 6–12 months starting 6 months post-RAI, more frequent for high-risk; US at 3 months (high-risk) or 6 months (low/intermediate-risk); TSH suppression: <0.1 mU/L (high-risk), 0.1–0.5 mU/L (intermediate), 0.5–2.0 mU/L (low-risk); for MTC, calcitonin and CEA monitoring, with calcitonin ≥150 pg/mL or doubling time indicating progression (Secs. 9.2, 2.3.2).

Abbreviations: ATA: American thyroid association; AUS: Atypia of undetermined significance; BRAF: B-Raf proto-oncogene; CAP: College of American Pathologists; CEA: Carcinoembryonic antigen; CLIA: Clinical Laboratory Improvement Amendments; cM1: Distant metastasis; mCi: Millicurie (unit of radioactivity); cN1: Regional lymph node metastasis; cN1a: Metastasis to level VI or VII lymph nodes; cN1b: Metastasis to unilateral, bilateral, or contralateral cervical compartments (levels I, II, III, IV or V) or retropharyngeal lymph nodes; cT1: Clinical tumor 2 cm or less in greatest dimension, limited to the thyroid; cT1aN0M0: Clinical tumor ≤1 cm in greatest dimension, limited to the thyroid, no lymph nodes, no metastases; cT1bN0M0: Clinical tumor >1 cm but ≤2 cm in greatest dimension, limited to the thyroid, no lymph nodes, no metastases; cT2: Clinical tumor >2 cm but ≤4 cm in greatest dimension, limited to the thyroid; cT3: Clinical tumor >4 cm in greatest dimension, limited to the thyroid or with gross extrathyroidal extension invading only strap muscles (sternohyoid, sternothyroid or omohyoid muscles); cT4: Clinical tumor with gross extrathyroidal extension that goes beyond the strap muscles; cN0: No regional lymph node metastasis; DATA framework: Diagnosis, risk/benefit assessment, treatment decisions, response assessment framework; DTC: Differentiated thyroid cancer; ¹⁸F-FDG PET/CT: Fluorine-18 fluorodeoxyglucose positron emission tomography/computed tomography; FLUS: Follicular lesion of undetermined significance; FN: Follicular neoplasm; FNA: Fine-needle aspiration; FNMTC: Familial non-medullary thyroid cancer; ¹²³I: Iodine-123; MEN-II: Multiple Endocrine Neoplasia type II; MTC: Medullary thyroid cancer; mU/L: Milliunits per liter; NHCPRC: National Health Commission of the People's Republic of China; PAX8/PPARγ: Paired box gene 8/peroxisome proliferator-activated receptor gamma; PEI: Percutaneous ethanol injection; PTC: Papillary thyroid cancer; PTMC: Papillary thyroid microcarcinoma; RAI: Radioactive iodine; RAS: Rat sarcoma; Rec.: Recommendation; RET/PTC: Rearranged during transfection/papillary thyroid carcinoma; RFA: Radiofrequency ablation; Sec.: Section; SFN: Suspicious for follicular neoplasm; SUSP: Suspicious for papillary carcinoma; TERT: Telomerase reverse transcriptase; Tg: Thyroglobulin; TgAb: Thyroglobulin antibody; TSH: Thyroid-stimulating hormone; US: Ultrasonography.

Table 3. Bethesda system categories and malignancy risks (2nd ed.ition)

Category	Frequency in FNA interpretation (%)	Malignancy risk (%)	Notes
Non-diagnostic	3–34	5–10	Repeat FNA with ultrasound guidance
Benign	60–70	0–3	Clinical follow-up unless symptomatic
AUS/FLUS	1–22	10–30	Repeat FNA or molecular testing (e.g., <i>Afirma</i> gene sequencing classifier, Thyroseq v3); potential lobectomy
FN/SFN	2–25 ¹⁰	25–40	Molecular testing; lobectomy
SFM	1–6	50–75 (~50% excluding NIFTP)	Immunohistochemistry/flow cytometry aids diagnosis for suspicious MTC/lymphoma, respectively; near-total thyroidectomy or lobectomy
Malignant	2–16	97–99	Includes PTC, MTC, PDTC, UTC, SQC, metastases; surgery tailored to subtype

Abbreviations: AUS/FLUS: Atypia of undetermined significance/follicular lesion of undetermined significance; FN/SFN: Follicular neoplasm/suspicious for follicular neoplasm; FNA: Fine-needle aspiration; MTC: Medullary thyroid carcinoma; NIFTP: Non-invasive follicular thyroid neoplasm with papillary-like nuclear features; PDTC: Poorly differentiated thyroid carcinoma; PTC: Papillary thyroid carcinoma; SFM: Suspicious for malignancy; SQC: Squamous cell carcinoma; UTC: Undifferentiated (anaplastic) thyroid carcinoma.

- *BRAF* V600E mutation has low sensitivity due to low-risk malignancies.
- Bethesda IV: FN/SFN (2–25% frequency,¹⁰ 25–40% malignancy risk): Includes Hürthle cell types (FN Hürthle cell type/suspicious FN Hürthle cell type, 10–40% malignancy risk). FNA cannot distinguish adenoma from carcinoma (most cases end up being adenomas instead of follicular carcinomas due to the proportions within the population); 27–68% of malignancies are PTC.
- Bethesda V: SFM (1–6% frequency, ~75% malignancy risk, ~50% excluding NIFTP): Includes suspicious for PTC, suspicious for MTC, suspicious for lymphoma, and suspicious for metastatic carcinoma. Limited use for ancillary molecular studies. Serum calcitonin testing and calcitonin immunoreactivity in suspected MTC, as well as flow cytometry for suspected lymphoma, aid diagnosis.
- Bethesda VI: Malignant (2–16% frequency, 97–99% malignancy risk): Primarily encompasses PTC (~85%

of cases, comprising a wide spectrum ranging from aggressive variants, such as tall cell and columnar cell types, to more indolent forms like the oncocytic variant, which behaves similarly to the classic and follicular type), followed by MTC (1–2%, plasmacytoid/spindle cells, calcitonin-positive, more aggressive and less differentiated than PTC or follicular carcinoma). Poorly differentiated thyroid carcinoma (0.3–6.7%, insular architecture) often metastasizes to regional lymph nodes, lungs, and bones, with a poor clinical prognosis (5-year survival ~50%). Undifferentiated (anaplastic) thyroid carcinoma (<5%, pleomorphic cells) is rarely seen in patients under 50 years and is associated with a poor prognosis, typically resulting in survival of 6 months to 1 year. Squamous cell carcinoma (<1%, pleomorphic keratinized cells) and metastases (e.g., from lung, breast, and melanoma) are also included.

5.2. Metastatic and rare tumors

Metastatic tumors of the thyroid are rare, but have been reported in up to 10% of cancer autopsies,⁴⁰ most often from lung, breast, kidney, colon, and melanoma, presenting as solitary, multiple, or diffuse nodules. FNA may mimic primary thyroid tumors; hence, clinical history and immunohistochemistry are critical: For example, metastatic renal cell carcinoma (RCC) is RCC antigen/cluster of differentiation (CD)10-positive and Tg/thyroid transcription factor-1-negative; melanoma is S100, SRY-box 10, human melanoma black, Melan A-positive; and breast carcinoma shows estrogen receptor, progesterone receptor, GATA-binding protein 3, mammaglobin positivity.¹³

Primary thyroid lymphomas, although uncommon, represent 1–5% of all thyroid neoplasms⁴¹ and are usually non-Hodgkin B-cell lymphomas, particularly diffuse large B-cell lymphomas and mucosa-associated lymphoid tissue, strongly linked to Hashimoto thyroiditis. Thyroid lymphoma cytology shows markedly cellular smears with non-cohesive lymphoid cells and lymphoglandular bodies. Mucosa-associated lymphoid tissue lymphomas have small- to medium-sized lymphocytes, while diffuse large B-cell lymphoma features large cells with prominent nucleoli. Because lymphoma often arises in Hashimoto thyroiditis, which shows a dense lymphoid infiltrate, distinguishing the two can be challenging; immunophenotyping or flow cytometry (e.g., CD20 positivity and light chain restriction) is essential for accurate diagnosis.^{13,41}

5.3. NIFTP and molecular testing

The 2016 reclassification of NIFTP as non-malignant⁴² has reduced overtreatment of low-risk lesions, lowering

malignancy risks in indeterminate categories such as AUS/FLUS, FN/SFN, and SFM, with SFM risk decreasing from approximately 75% to around 50%.¹³ Similarly, although not included in the Bethesda System, the updated Porto Proposal^{43,44} suggests reclassifying certain low-risk PTMCs as papillary microtumors to avoid overtreatment. This reclassification aims to better identify indolent tumors that may not require aggressive management, though widespread adoption and formal reclassification of PTMCs remain under evaluation.⁴⁵

Molecular testing, notably the current platforms Afirma GSC and ThyroSeq v3, is particularly useful in cytologically indeterminate categories (Bethesda III and IV) where cytology alone cannot reliably predict malignancy. For AUS/FLUS, the 2015 ATA guidelines recommend conservative management with either repeat FNA or molecular testing, as a second aspirate often yields a more definitive diagnosis.¹⁰ Mutational analysis with *BRAF* V600E has low sensitivity, and while expanded mutation panels increase detection rates, they reduce specificity due to the frequent presence of *RAS* mutations.^{13,46} The earlier Afirma GEC offered the greatest diagnostic value in this setting: A negative result reduces the risk of malignancy from 24% to 5%, supporting observation over surgery in many patients, particularly those with isolated architectural atypia.^{13,47}

Current NGS panels (Afirma GSC and ThyroSeq v3), which have replaced the older Afirma GEC and ThyroSeq v2 platforms, substantially expand the proportion of indeterminate nodules that can be safely managed non-operatively. They achieve higher benign call rates and preserve NPVs (>94%), allowing observation or active surveillance in a significantly larger fraction of Bethesda III/IV nodules than was possible with the GEC.^{33–36} Similarly, in FN/SFN (Bethesda IV) nodules, molecular testing complements clinical and imaging data. The earlier Afirma GEC, which was the first commercially available test, categorized an aspirate as either “benign” or “suspicious” by analyzing the expression profile of over 100 genes, adding particular value by recognizing parathyroid signatures that might otherwise confound the diagnosis. Both the Afirma GSC and ThyroSeq v3 offer improved performance compared to the earlier versions. For Hürthle cell neoplasms, the Afirma GEC identified approximately 39% of these nodules as benign, reducing unnecessary surgeries in up to one-third of patients while preserving an NPV of ≥94%, though suspicious results add little beyond cytology.⁴⁸ The newer panels markedly increase benign call rates (56–84% vs. ~39% with GEC), enabling avoidance of surgery in the majority of cases without compromising detection of malignancy.³⁶ Afirma additionally incorporates

a dedicated MTC classifier, which effectively identifies MTC among indeterminate nodules.⁴⁹

For NIFTP and the non-invasive follicular variant of PTC, molecular profiling is useful. *RAS* mutations are common, *PAX8/PPARG* translocations, *THADA* fusions, and *BRAF* K601E mutations occur occasionally, while *BRAF* V600E mutations and *RET* fusions are absent, helping to separate these from conventional PTC. However, it is still uncertain if molecular testing will effectively identify NIFTP nodules in a prospective manner when the appropriate clinical and cytological context is provided.¹³

By contrast, in the SFM category, particularly when suspicious for PTC, molecular testing and Afirma contribute little to diagnosis because the malignancy risk is already high. Mutational testing (e.g., *BRAF*, *RAS*, *RET/PTC*, *PAX8/PPARG*) is not routinely recommended, except selectively when results may influence management decisions.¹⁰ In this setting, ancillary studies are more decisive: calcitonin and related immunostains confirm MTC, while flow cytometry provides definitive characterization of lymphoma.¹³ Finally, in anaplastic thyroid carcinoma, molecular analysis remains informative, consistently showing *TP53* (80%), *CTNNB1* (β -catenin) (70%), *RAS* (50%), and *BRAF* V600E (30%) mutations that illustrate the stepwise progression from early drivers (*RAS* and *BRAF*) to late events (*TP53* and *CTNNB1*) causing dedifferentiation.¹³

5.4. Updates on Bethesda system and WHO classification of tumors in thyroid cytopathology

The Bethesda System facilitates standardized thyroid FNA interpretation, enhancing communication among pathologists, endocrinologists, radiologists, and surgeons. The 2023 third edition of the Bethesda System⁵⁰ introduced refinements, including single definitive names for its six diagnostic categories: (I) non-diagnostic, (II) benign, (III) AUS, (IV) FN, (V) SFM, and (VI) malignant. This update eliminates alternate category names to reduce confusion. In addition, the revised edition provides updated and more accurate risk of malignancy estimates based on recent data. The AUS category is further stratified into two subgroups—nuclear atypia and other atypia—each associated with different risks of malignancy and distinct molecular profiles. Terminology has been aligned with the 2022 WHO Classification of Thyroid Tumors, enhancing clarity and clinical relevance. New chapters addressing pediatric thyroid disease, clinical perspectives, imaging modalities, and the expanding role of molecular and ancillary testing have also been incorporated. Together, these updates aim to improve diagnostic precision and inform better management strategies for thyroid nodules, especially within the indeterminate categories

where diagnostic uncertainty has historically been a challenge.^{51–53}

It should be noted that the detailed category prevalence and malignancy risks provided in Section 5.1 and Table 3 are based on the second edition of the Bethesda System (2017), as reflected in currently available data. The 2023 third edition, now emerging in clinical practice, further refines terminology and risk stratification, with updated risk of malignancy values and structural changes designed to improve clinical utility and molecular integration. Readers interested in the latest Bethesda recommendations are encouraged to consult the new edition directly. However, the core diagnostic framework and categories remain consistent between editions.

The Endocrine and Neuroendocrine Tumors volume in the WHO Classification of Tumors, fifth edition (Volume 10),⁵⁴ is part of a multi-volume series released by WHO over several years, with initial volumes published starting in 2019. Each volume is published individually on completion. The Endocrine and Neuroendocrine Tumors volume, which includes the thyroid, was finalized and made available online in 2022, allowing early access and citation by the scientific and clinical community.⁵⁵ The official print edition was published in March 2025. It introduces a more nuanced classification of thyroid tumors, incorporating benign, low-risk, borderline, and malignant categories. Notably, the WHO classifies follicular cell-derived neoplasms into benign, borderline/low-risk, and malignant entities with detailed histologic and molecular criteria. It introduces new tumor types, such as differentiated high-grade thyroid carcinoma, alongside traditional poorly differentiated thyroid carcinoma, and includes strict diagnostic criteria for NIFTP with no changes from prior definitions but expanding recognized subtypes (e.g., oncocytic NIFTP and subcentimeter NIFTP). The WHO emphasizes molecular alterations correlated with tumor types, supporting integrated histomolecular diagnosis that enhances risk stratification and personalized treatment approaches. Pathologists are encouraged to adopt this updated classification to improve diagnostic precision and prognostication.⁵²

The combination of updated Bethesda cytology reporting and the WHO tumor classification, as integrated into the 2025 ATA guidelines,¹¹ reflects a shift toward refined, molecularly informed diagnoses aimed at reducing overdiagnosis and overtreatment while identifying tumors with aggressive potential. This integrated approach highlights the importance of molecular testing in indeterminate cytology cases, optimizing patient outcomes and tailoring management strategies. However, ongoing validation and clinical correlation remain necessary to

fully realize the promise of these advanced classification systems.⁵⁶

6. Management of PTMCs

Defined as PTCs ≤ 1 cm in greatest dimension, PTMCs have driven the thyroid cancer epidemic, increasing from 25% of diagnoses in 1988 to 39% in 2008, and up to 47.5% in 2016.² Despite ATA recommendations that diagnostic FNA should not be performed for nodules < 1 cm, a survey showed that 67% of clinicians reported performing FNA on subcentimeter nodules with suspicious sonographic features, contributing to potential overdiagnosis,^{38,39} as indicated earlier in Section 4. This practice persists due to concerns about missing aggressive cancers, despite evidence that most PTMCs are indolent. Nevertheless, active surveillance is increasingly accepted for low-risk PTMCs, with studies reporting:

- Lymph node metastases in 1.6% (95% CI: 1.1–2.4%) at 5 years and 3.4–3.8% at 10 years^{57,58}
- Tumor growth (> 3 mm) in 8–10% of cases at 10 years^{37,58,59}
- Mortality risk < 1 in 1,000.³⁷

Risk stratification considers sonographic features, such as extrathyroidal extension (associated with worse outcomes⁶⁰), proximity to critical structures (e.g., trachea and recurrent laryngeal nerve), and lymph node involvement.^{10,12} Patient age is also a significant factor, with younger patients (< 40 years) showing slightly higher progression rates, though active surveillance remains beneficial, as delayed surgery does not increase risk.⁶¹ Nodule size alone is a poor predictor of malignancy, with no increased risk beyond 2–4 cm.^{62,63} However, once cancer has been confirmed, larger tumor sizes correlate with higher rates of recurrence and nodal involvement. Therefore, understanding the context is crucial when evaluating the implications of nodule size in relation to malignancy. The 2015 ATA guidelines further emphasize this point by recommending surgery for benign nodules > 4 cm only if symptomatic (e.g., dysphagia and hoarseness), while noting that this recommendation is supported by low-quality evidence.

Active surveillance protocols typically involve ultrasonography monitoring every 6–12 months to assess nodule growth or lymph node involvement. However, patient anxiety during surveillance, driven by fears of “missed” malignancies, remains a significant barrier.⁶⁴ Clinicians must provide robust counseling, emphasizing the low progression and mortality risks. For example, a study found no difference in cancer risk between solitary and multiple nodules, suggesting that multifocality alone does not necessitate surgery.⁶⁵ Surgical options for PTMCs include lobectomy or total thyroidectomy, with the 2015

ATA guidelines favoring lobectomy for low-risk cases to minimize complications.¹⁰ However, total thyroidectomy facilitates post-operative monitoring with serum Tg, which is less reliable post-lobectomy.⁶⁶ This trade-off complicates decision-making, as Tg monitoring may prompt unnecessary interventions for trace levels that are not clinically significant.

Emerging alternatives, such as RFA, microwave ablation, and laser ablation (LA), have shown reliable efficacy and safety in treating T1N0M0 PTC. RFA demonstrated advantages in volume reduction rate at 12 months, lower complication rates, and fewer LNMs, while LA achieved the highest complete disappearance rate.⁶⁷ Long-term 10-year follow-up shows that RFA for low-risk PTMC achieves complete disappearance of treated tumors with no local progression or metastasis.⁶⁸ While 7.7% of patients developed new PTCs distinct from the ablated lesions, this reflects the multifocal nature of the disease rather than treatment failure, supporting RFA as a safe and minimally invasive alternative to surgery in carefully selected patients.

7. Lymph node metastases and recurrence

Due to the inclusion of diverse types of thyroid cancer and heterogeneous risk cohorts within studied populations, there is considerable variability and uncertainty in reported LNM rates. For example, the incidence of central LNM (CLNM) ranges from approximately 33% in PTMC^{69,70} to between 20% and 66% in other PTC cohorts,⁶⁴ and overall PTC populations show an even wider reported prevalence range of 30–80%,⁷¹ reflecting differences in tumor size, detection methods, study populations, and metrics used. In addition, it has been reported that 30–65% of patients with clinically node-negative (cN0) PTC are found to have CLNM on pathological examination after surgery, despite no clinical or radiological evidence of lymph node involvement before surgery.^{71,72}

In a recent cross-sectional study of 346 cN0 PTC patients undergoing transoral endoscopic thyroidectomy vestibular approach (TOETVA), occult CLNM was found in 39.9%,⁷³ consistent with previous reports. This study identified young age (< 29 years), tumor size > 6.5 mm, and gross extrathyroidal extension as independent risk factors for higher CLNM incidence and burden, underscoring the importance of individualized risk stratification to guide the extent of surgery. TOETVA was demonstrated to provide effective prophylactic central neck dissection with favorable cosmetic and oncological outcomes, supporting the selective use of prophylactic central neck dissection in patients with these risk factors.

An earlier retrospective study by Wang *et al.*⁷⁴ involving 508 patients with well-differentiated thyroid carcinoma

reported that 9% had palpable lateral cervical LNMs at the time of surgery, with a higher prevalence among patients younger than 45 years. Despite the frequent presence of occult microscopic nodal metastases among cN0 patients who did not undergo initial neck dissection, the clinical recurrence rate in the lateral neck for this cohort was low (3%), particularly in younger individuals. They found that larger tumor size (>4 cm) and age ≥45 years were associated with an increased risk of nodal recurrence and higher disease-specific mortality. These findings support current guidelines that discourage routine aggressive intervention for occult lateral LNMs, recommending more targeted surgery and adjuvant therapy in higher-risk cohorts.

In this context, the practice of prophylactic central lymph node dissection (CLND) in clinically cN0 patients is a subject of significant debate. Some studies support routine CLND, citing high LNM rates (40–90% in PTC) and potential recurrence prevention, particularly in young males with cN0 PTC.^{64,75,76} Others argue that extensive CLND offers no survival benefit and is associated with increased complications, including hypoparathyroidism in approximately 20% of cases and an overall complication rate of about 44%. Moreover, recurrence rates are comparable between patients undergoing prophylactic CLND—around 4.5% for clinically cN0 PTC—and those managed without prophylactic surgery, with recurrence rates ranging from 2% to 6% in PTMC cases, highlighting the need for risk stratification.^{10,77–79} Similar results have been obtained in 259 PTMC cases, where 235 patients underwent prophylactic node dissection.⁷² No significant difference was observed in terms of recurrence when compared with a reference group of 155 PTMC patients who did not undergo lymph node dissection, indicating that the procedure is not beneficial in cN0 cases with low-risk PTCs.

In contrast, recent studies show more moderate risks for thyroidectomy complication rates, with Javidi *et al.*⁸⁰ reporting recurrent laryngeal nerve injury at about 6.1% and hypocalcemia significantly higher after total versus subtotal thyroidectomy. Meanwhile, Getachew *et al.*,⁸¹ in a systematic review and meta-analysis focused on surgically treated thyroid disease in Africa, found a pooled complication prevalence of 26.6%, with hypoparathyroidism occurring in 8.5% of cases and nerve injury in 8%. These findings highlight the variability in complication rates, which can differ significantly based on the extent of surgery, such as total versus subtotal thyroidectomy, as well as factors like surgeon experience and regional healthcare context. Notably, recent data indicate that specialized high-volume centers can achieve considerably lower complication rates—often below 2–4% for permanent hypoparathyroidism or recurrent laryngeal

nerve injury—compared to the higher rates observed in low-volume or resource-limited settings.^{82,83}

A balanced perspective suggests that CLND may be warranted in high-risk cohorts but remains contentious for most PTC presentations.^{70,71} The ATA guidelines^{10,11} recommend a selective approach to prophylactic CLND. Specifically, prophylactic CLND is strongly recommended, with moderate-quality evidence, not to be performed in most patients with small, non-invasive cT1-T2 cN0 PTC and in most follicular thyroid cancers, given the lack of survival benefit and the potential for added surgical morbidity. However, CLND may be considered in patients with advanced primary tumors (T3 or T4) or in cases where information on nodal status is needed to guide subsequent therapeutic decisions, such as adjuvant RAI use or surveillance strategies. The latter, however, is a conditional recommendation supported by low-quality evidence, reflecting the balance between possible staging and therapeutic benefits against the risks of surgical complications. Ultimately, the decision should be individualized and weighed against the increased risk of hypoparathyroidism and recurrent laryngeal nerve injury, with the strongest rationale for prophylactic surgery seen in selected high-risk patients rather than in the broader cN0 PTC population.

Active surveillance studies report low LNM rates in microcarcinomas of the thyroid gland: 1.6% at 5 years and 4% at 10 years^{37,57} (Table 4). Importantly, LNM does

Table 4. Outcomes of active surveillance versus surgery for low-risk PTMCs

Outcome	Active surveillance	Surgery (lobectomy/total thyroidectomy)
Lymph node metastases ^a	1.6–4% at 5–10 years ^{37,57}	2–6% recurrence ¹⁰
Tumor growth (>3 mm)	4–8% at 10 years ^{37,58,59}	Not applicable
Mortality risk	<1 in 1,000 ³⁷	Negligible ¹⁰
Complications	Minimal (anxiety) ^{64b}	Hypoparathyroidism 8.5%, nerve injury 6–8%, ^{80,81} but rates can often be below 2–4% for permanent complications in high-volume centers ^{82,83}

Notes: ^aThe lower values observed for active surveillance outcomes reflect the fact that patients selected for this approach are highly chosen from low-risk cohorts. These cases typically involve small, well-defined tumors with minimal risk factors, making disease progression less likely and recurrence rates lower compared to surgical groups where patient risk profiles may be more varied. ^bSome patients—particularly younger individuals—experience higher anxiety and emotional distress during surveillance, related to the uncertainty of living with untreated cancer. Psychological counseling and supportive interventions may be necessary to help manage these effects and improve quality of life during follow-up. Abbreviation: PTMC: Papillary thyroid microcarcinoma.

not significantly affect overall survival in PTC, with the 2015 ATA guidelines noting a “small” effect.¹⁰ Dr. Blake Cady’s⁸⁴ seminal work emphasizes that “regional lymph nodes are indicators, not governors of survival,”^{84(p185)} challenging aggressive lymph node dissections. He further highlights that the absence of distant organ metastases in such cases reflects metastatic specificity rather than lethality, suggesting that lymph node involvement is often biologically distinct from systemic spread. As Cady notes, this perspective “hopefully will help place the role of LNMs generally and their surgical removal on a more scientifically and logically based understanding.”^{84(p185)} Building on this concept, he proposed that “the future may allow us to abandon some aspects of our surgical or systemic attack on clinical cancer metastases, such as lymph node removal.”^{84(p185)} This view aligns with a broader understanding in oncology regarding the relative importance of nodal disease compared with distant metastases.^{85,86} Emerging evidence even supports active surveillance for small metastatic lymph nodes in select patients, with no increased risk compared to immediate surgery.⁸⁷ However, caution is warranted, as long-term data remain limited, and careful patient selection, consistent monitoring, and individualized risk assessment are critical to ensuring safety in the application of surveillance-based strategies.

A similar concern regarding overtreatment has been highlighted by Grant⁷⁸ in a comprehensive review. He observed that advances such as high-resolution ultrasonography and highly sensitive stimulated Tg assays led to a climate where even the smallest residual or microscopic evidence of disease generated considerable anxiety in both physicians and patients, often driving interventions of questionable necessity. As already mentioned, recurrence risks are low in low-risk PTC, with loco-regional recurrence rates of 2–6% following thyroid surgery without neck dissection.¹⁰ In contrast, extensive lymph node dissections do not eliminate recurrence (2% per year) and increase morbidity.⁷⁸ For example, Mazzaferri *et al.*⁷⁹ reported that extensive dissections were associated with significant complications without preventing recurrence. These findings underscore the need for a risk-stratified approach, prioritizing surveillance or limited surgery (e.g., lobectomy) for low-risk PTMCs while reserving aggressive interventions for high-risk cases, such as those with extrathyroidal extension or distant metastases. The rarity of distant metastases in most PTC cases supports a conservative management approach, reflecting the limited metastatic specificity of lymph node involvement, which typically remains confined to regional spread without progressing to distant organs.⁸⁴

8. RFA for thyroid nodules

The escalating incidence of thyroid nodules, particularly low-risk PTMCs, has intensified the search for management strategies that balance efficacy with minimal invasiveness, a central theme in the effort to curb overtreatment. RFA has emerged as a compelling approach, offering a minimally invasive option to reduce nodule volume and alleviate symptoms without the complications associated with thyroidectomy, such as hypoparathyroidism, recurrent laryngeal nerve injury, and an overall complication rate that can be as high as 26.6%, as highlighted in recent meta-analyses and summarized in this review.⁸¹

By delivering high-frequency alternating current through a thin electrode, RFA generates localized heat to ablate targeted thyroid tissue, consistent with conservative management strategies like active surveillance for low-risk PTMCs.^{10-12,37} As a recognized minimally invasive treatment, RFA is particularly effective for benign thyroid nodules causing compressive symptoms such as dysphagia and dyspnea or cosmetic concerns, which often do not require surgery due to their indolent nature. Multiple international clinical guidelines, including those reviewed by Lee *et al.*,⁸⁸ support RFA for nodules confirmed benign cytologically, recommending ultrasonography-guided techniques such as the transisthmus approach and moving-shot technique. RFA has proven to be safe and effective, offering significant volume reduction and symptom relief with low complication rates. Differences in guidelines exist, but they generally align on indications and procedural standards, pointing to a need for unified international recommendations.

The 2020 European Thyroid Association guideline⁸⁹ notes that thermal ablation, including RFA and LA, should be reserved for benign thyroid nodules causing symptoms or aesthetic issues. Ethanol ablation remains preferred for cystic nodules due to its cost-effectiveness, while microwave ablation and high-intensity focused ultrasound are emerging, though they require further assessment. Treatment choice must consider patient preferences, nodule characteristics, and available expertise; however, clinicians should also be aware of potential complications of RFA, such as voice changes and tumor rupture, although rare, and manage them appropriately.⁹⁰

The RFA approach is also increasingly explored for low-risk PTMCs in patients who are poor surgical candidates—due to comorbidities or advanced age—or those who prefer to avoid surgery’s lifelong consequences, such as thyroid hormone replacement.⁹¹⁻⁹³ In these cases, RFA has shown favorable efficacy in both the short and mid-to-long terms, with minimal complications, proving safe and effective even in older patients who are

at higher risk of surgical complications; however, active surveillance remains the preferred first-line alternative to surgery, and long-term data beyond 10 years are still limited. In addition, RFA shows promise in managing small recurrent thyroid cancers, such as LNMs, where repeat surgery poses significant risks.^{94,95} Performed under ultrasound guidance with local anesthesia, the outpatient procedure allows precise targeting, minimizing damage to surrounding tissues and enabling rapid recovery, which enhances its appeal for patients wary of surgical morbidity.

These outcomes highlight RFA's ability to address both functional and aesthetic concerns while preserving thyroid function, a critical advantage over more aggressive surgical interventions that frequently result in loss of thyroid function and the need for lifelong hormone replacement. Nonetheless, while 5-year follow-up data demonstrate encouraging durable outcomes,⁹³ further longer-term studies, standardized treatment protocols, and comparative trials with surgery remain necessary to fully establish its durability and optimal role in PTMC management.⁹² The procedure's repeatability further enhances its utility, allowing additional sessions for incomplete ablation or new nodules, supporting long-term management without invasive interventions.

However, RFA's application is not without challenges. The procedure's success is heavily operator-dependent, requiring specialized training in ultrasonography-guided techniques, which may restrict access in non-specialized centers without adequate standardization and multicenter validation.⁹⁶ Moreover, while the 2025 ATA guidelines explicitly endorse ultrasonography-guided percutaneous ablation, including RFA, as an alternative to active surveillance or resection for cT1aN0M0 PTMCs in selected patients (Recommendation 11B) and for recurrent or residual thyroid cancer in patients at high risk for reoperation complications (Recommendation 52[3]), these recommendations are conditional because the certainty of evidence is low, which creates a gap between practice in specialized centers and cautious guideline implementation due to limited long-term data.

In summary, RFA's narrative within thyroid nodule management is one of cautious optimism. It offers a patient-centered approach that reduces the physical and psychological burdens of surgery, resonating with the review's goal of minimizing overtreatment for low-risk PTMCs. As evidence accumulates and techniques refine, RFA and related approaches may find a more defined place in clinical guidelines, potentially transforming the management of low-risk thyroid nodules into a less invasive, more personalized paradigm.

9. Tg in dynamic risk stratification: Value and difficulties

Serum Tg, a glycoprotein secreted exclusively by thyroid follicular cells, is a cornerstone biomarker in the 2025 ATA guidelines for DTC.¹¹ Its measurement underpins dynamic risk stratification, a strategy that refines recurrence risk assessment over time by integrating Tg with imaging, histopathology, TgAb, and clinical outcomes. This approach enables clinicians to individualize post-treatment monitoring and management, balancing the detection of persistent or recurrent disease with the need to avoid overtreatment, particularly in low-risk PTMCs.

The 2025 ATA guidelines emphasize Tg in multiple phases of care. Postoperatively, Recommendation 28 indicates integrating Tg levels with histopathological features, imaging, and TgAb into the ATA Risk Stratification System to estimate the likelihood of structural persistence or recurrence. Recommendation 29 incorporates Tg into the ATA Response Criteria, categorizing patients into excellent, indeterminate, biochemical incomplete, or structural incomplete response groups that guide surveillance intensity and further therapy. Recommendation 30 strongly supports Tg measurement within 6–12 weeks after total thyroidectomy, regardless of whether the patient is on thyroid hormone therapy or undergoing TSH stimulation, to shape early follow-up decisions, with a single Tg measurement recommended for lobectomy patients under normal TSH to detect unexpected elevations, albeit with cautious interpretation due to residual thyroid tissue.

Long-term monitoring is specified in Recommendation 47, which advocates Tg testing every 6–12 months post-total thyroidectomy, with increased frequency for intermediate- or high-risk groups, and no routine Tg assessment after lobectomy during initial follow-up; in TgAb-positive patients, serial antibody trends with a consistent assay and imaging guide surveillance. Recommendation 48 further refines this by permitting low-risk DTC patients with durable excellent responses after 5–8 years to limit surveillance to biochemical markers alone every 1–2 years, with biochemical testing discontinued after 10–15 years when complete remission is evident. In this regard, the 2015 ATA guidelines¹⁰ continue to provide valuable guidance for certain patient groups, particularly for individuals treated with lobectomy or without RAI. Recommendation 64 advises periodic serum Tg monitoring on thyroid hormone therapy in such patients to detect rising trends, while Recommendation 63 specifies Tg testing at 6–18 months after remnant ablation (via sensitive assays or TSH stimulation) to verify disease absence.

Within this broader context, Tg's role in dynamic risk stratification is to categorize patients into response groups at key intervals, typically 6–24 months post-treatment. An undetectable stimulated Tg level (<0.2 ng/mL) following total thyroidectomy and RAI signals an excellent response, indicating minimal residual disease or recurrence risk, supporting reduced follow-up. Conversely, elevated stimulated Tg (>1 ng/mL) or rising levels without structural disease suggest a biochemical incomplete response, necessitating closer monitoring, while structural disease on imaging, often with high Tg levels, indicates a need for intervention.⁹⁷

In low-risk PTMCs managed with active surveillance as an alternative to immediate surgery, serial ultrasonography is the primary tool to monitor tumor growth or LNM, with periodic serum Tg measurements providing supportive evidence for the safety of observation, though limited by normal thyroid tissue or TgAb interference. Rising Tg levels may warrant additional evaluation, such as ultrasonography or, in specific cases, FNS-washout Tg (FNA-Tg) to assess for tumor progression or metastases. Tools like the thyroid cancer care collaborative (TCCC) facilitate consistent monitoring by standardizing ultrasound reporting and tracking patient data. Challenges, including patient adherence and the need for standardized ultrasound protocols, highlight the importance of robust systems like the TCCC to ensure effective active surveillance.^{97,98}

However, the narrative of Tg's utility is complicated by significant difficulties that undermine its reliability, particularly in low-risk PTMCs managed with lobectomy or active surveillance, where small changes in Tg levels can precipitate clinical uncertainty and patient anxiety.^{64,66} Tg's promise is overshadowed by a series of challenges that confound its interpretation, especially in low-risk settings. TgAb, present in up to 25% of DTC patients during initial post-operative evaluation,⁹⁹ significantly interferes with serum Tg measurements. These antibodies can either mask the presence of disease by causing falsely low or undetectable Tg values or, less commonly, produce falsely elevated Tg levels (such as via the presence of heterophilic antibodies¹⁰⁰), both of which can lead to misinformed clinical decisions and inappropriate management. Importantly, TgAb interference cannot be fully overcome by current assay designs, and even highly sensitive tests such as mass spectrometry may underestimate Tg in TgAb-positive patients.

The 2015 and 2025 ATA guidelines^{10,11} address these challenges by prioritizing imaging over Tg measurements in scenarios where Tg reliability is compromised, particularly in low-risk PTMCs and TgAb-positive patients.

For low-risk PTMCs managed with active surveillance, the 2025 guidelines (Recommendations 11A, 12–14) recommend ultrasonography as the primary surveillance tool, explicitly advising against routine Tg and TgAb testing (Recommendation 13) to avoid uncertainty and anxiety from Tg fluctuations, with surgical intervention reserved for disease progression or patient preference (Recommendation 14).

When Tg levels are elevated, or TgAb is present with negative or equivocal ultrasound findings, the guidelines recommend additional imaging to clarify disease status. The 2025 guidelines (Recommendation 31B, 31F, and 31G) suggest cross-sectional imaging (e.g., CT or magnetic resonance imaging [MRI]). ¹⁸F-FDG PET/CT is indicated in high-risk oncocytic or poorly differentiated thyroid carcinomas. The 2015 guidelines (Recommendation 68) similarly endorse ¹⁸F-FDG PET/CT for high-risk DTC patients with elevated Tg (>10 ng/mL) and negative RAI imaging. Historically, radionuclide imaging, as described by Maxon,¹⁰¹ provides a complementary approach for intermediate-to-high risk cases, with ¹²³I or low activity ¹³¹I whole-body scans detecting iodine-avid disease in up to 90% of cases with adequate serum TSH concentrations (2015 Recommendation 67; 2025 Recommendation 49C). However, for non-iodine-avid disease, Maxon¹⁰¹ suggests thallium-201 chloride or technetium-99m-MIBI SPECT, highlighting the limited availability of FDG-PET at the time. The ATA guidelines favor ¹⁸F-FDG PET/CT due to its higher sensitivity and specificity (2015 Recommendation 68; 2025 Recommendation 50) for high-risk cases. These imaging strategies mitigate the limitations of Tg in TgAb-positive patients based on adequate risk stratification.

Assay variability further complicates the clinical interpretation of Tg, as different assays possess distinct sensitivity thresholds ranging from 0.1 to 1.0 ng/mL and variable specificity across laboratories. This variability leads to inconsistencies in Tg measurements that undermine reliable trend analysis, which is critical for dynamic risk stratification in DTCs monitoring.^{102,103} Moreover, the absence of complete international standardization of Tg assays exacerbates these discrepancies, posing significant challenges for multicenter studies and clinical consistency.

In patients managed with lobectomy, increasingly favored for low-risk PTMCs,^{10,11,66} or those with residual thyroid tissue post-surgery, Tg levels may reflect benign remnant tissue rather than malignancy, rendering recurrence detection unreliable. This is equally problematic in active surveillance, where the intact thyroid gland's natural Tg production obscures malignant contributions, making small fluctuations difficult to interpret and potentially triggering unnecessary imaging or intervention,

thus risking overtreatment. The timing of Tg measurements adds another layer of complexity; early post-surgical measurements may overestimate Tg due to inflammation or remnant tissue, while delayed measurements risk missing early recurrence, and no standardized schedule exists for active surveillance.^{104,105} The choice between stimulated Tg (post-TSH stimulation, more sensitive but invasive and costly) and unstimulated Tg (convenient but less sensitive) further complicates follow-up, particularly for low-risk PTMCs where detecting subclinical disease is critical yet patient comfort is paramount.¹⁰³

In active surveillance, the lack of clear Tg thresholds for intervention amplifies these challenges, as small increases may reflect physiological variation rather than progression, yet can heighten patient anxiety and prompt overtreatment, undermining the review's conservative management goals.⁶⁴ Consequently, Tg should not be used in isolation; it must be interpreted in conjunction with neck ultrasound. When indicated, cross-sectional imaging such as neck CT or MRI, as well as other relevant biomarkers like calcitonin for medullary thyroid cancer, should be implemented to provide a comprehensive context for disease monitoring and recurrence detection.¹⁰⁶ Patient education on its uncertainties, and advocacy for assay standardization to realize its full potential in minimizing overtreatment while ensuring timely intervention for aggressive cases should be prioritized.

10. Discussion

This review highlights the high prevalence of incidental thyroid cancer in autopsy studies, supporting the notion that many cases are indolent and do not require intervention. Overdiagnosis, driven by widespread ultrasonography and FNA, has led to overtreatment of low-risk PTMCs, prompting guideline shifts toward active surveillance. The Bethesda System aids risk stratification, but indeterminate categories (AUS/FLUS, FN/SFN, and SFM) complicate management due to variable malignancy risks, necessitating improved molecular diagnostics. Controversies surrounding prophylactic CLND reflect the balance between preventing recurrence and minimizing surgical morbidity.

10.1. Clinical implications

Clinicians should prioritize risk stratification, limiting FNA to nodules with high-risk features (e.g., history of radiation exposure, familial syndromes, lymph node involvement, and elevated calcitonin) and considering active surveillance for low-risk PTMCs. The 2022 NHCPRC guidelines provide clear criteria for surveillance, emphasizing single lesions <1 cm in central thyroid locations without metastases,¹² while the 2025 ATA guidelines conditionally extend this recommendation with

low-certainty evidence to select patients with cT1N0M0 PTCs.¹¹ Patient education is critical to address anxiety during surveillance, which can be exacerbated by fears of progression.⁶⁴ Counseling should emphasize the low progression (1.6–4% at 5–10 years) and mortality risks (<1 in 1,000) in low-risk PTMCs.^{37,57} Multidisciplinary teams, including endocrinologists, surgeons, and psychologists, can enhance shared decision-making.

Cost-effectiveness is a key consideration. Active surveillance reduces healthcare costs compared to surgery, which involves hospitalization, hormone replacement, and potential complications. Studies suggest that surveillance is an economically favorable strategy for low-risk PTMCs, particularly in resource-constrained settings, and report a similar risk of developing nodal metastases in those who underwent active surveillance compared to those who were treated with surgery on diagnosis.^{58,107} However, adherence to guidelines remains a challenge, as evidenced by the 67% of clinicians willing to perform FNA on subcentimeter nodules despite recommendations.^{38,39} Clinician education, decision-support tools, and policy interventions are needed to align practice with evidence.

Emerging strategies, such as RFA, offer minimally invasive alternatives for low-risk PTMCs, particularly for patients unsuitable for surgery or surveillance.^{91–93} RFA uses thermal energy to ablate nodules, preserving thyroid function, but long-term outcomes require further study. Similarly, dynamic risk stratification using serum Tg can guide follow-up, though its utility is limited post-lobectomy due to residual thyroid tissue.⁶⁶ These approaches highlight the need for personalized management plans tailored to patient risk profiles and preferences.

10.2. Research gaps

Standardized autopsy protocols are needed to clarify iDTC prevalence, as variability in examination thoroughness affects estimates.^{7,8,20} Further research should refine risk stratification for indeterminate FNA results, potentially through NGS or expanded molecular panels. Long-term outcomes of active surveillance in diverse populations, including those with small metastatic lymph nodes, require evaluation to confirm safety and efficacy.⁸⁷ Comparative studies of regional screening practices (e.g., South Korea vs. China) could inform global guidelines, addressing disparities in overdiagnosis.³⁴ Cost-effectiveness analyses of surveillance versus surgery or RFA are also needed to guide resource allocation.¹⁰⁷

10.3. Author's perspective

The evidence suggests that overtreatment of low-risk thyroid cancers, driven by fear of rare aggressive cases, outweighs benefits for most patients. The risk of rapid progression

in low-risk PTMCs under active surveillance is estimated to be 1–5%, with tumor enlargement and development of LNM occurring in a minority of patients over years of follow-up.^{105,108,109} Thus, aggressive surgery for all cases risks unnecessary harm (e.g., hypoparathyroidism and vocal cord paralysis) in the majority.^{37,78} This approach is difficult to justify when active surveillance achieves comparable outcomes with minimal risk.^{57,58} Patient anxiety during surveillance, cited as a barrier to conservative management,⁶⁴ can be mitigated through better education about the indolent nature of PTMCs and the minimal impact of LNM on survival.^{10,84} For low-risk cases, lobectomy may be preferred over total thyroidectomy to avoid complications and simplify follow-up, since serum Tg is less reliable post-lobectomy.⁶⁶ However, case-by-case evaluation is essential, as factors such as extrathyroidal extension or patient preference may warrant more aggressive diagnostic or therapeutic interventions. These strategies align with the principle of minimizing harm while ensuring timely intervention for rare aggressive cancers, supported by the low recurrence rates and negligible mortality in low-risk PTMCs.³⁷

11. Conclusion

The rising incidence of thyroid cancer, predominantly PTMCs, is largely a diagnostic artifact driven by excessive ultrasonography and FNA use, as evidenced by autopsy studies showing a 4–36% prevalence of indolent iDTC. The 2015 and 2025 ATA and 2022 NHCPRC guidelines endorse active surveillance for low-risk PTMCs, supported by low progression rates and negligible mortality (<1 in 1,000). The Bethesda System enhances risk stratification, yet indeterminate categories underscore the need for advanced molecular diagnostics. Debates over LNMs highlight the value of selective, risk-stratified interventions, favoring surveillance or limited surgery over aggressive approaches. Emerging modalities, such as RFA and dynamic Tg monitoring, offer promising alternatives but require further validation and standardization. To curb overtreatment, clinicians must prioritize guideline adherence, patient education to alleviate anxiety, and refined risk stratification, ensuring timely intervention for aggressive cases while upholding the principle of minimizing harm.

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