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Anti-Thyroglobulin Antibodies as a Surrogate Tumor Marker for the Follow-Up of the Differentiated Thyroid Carcinoma: Clinical Implications and Pitfalls

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Antithyroglobulin antibodies (TgAb) are present in 10–25% of patients with differentiated thyroid cancer (DTC) and significantly affect the reliability of serum thyroglobulin (Tg) measurements during follow-up. Beyond causing assay interference, TgAb have emerged as independent surrogate tumor markers with prognostic implications. This review summarizes the current evidence on antithyroglobulin antibody biology, measurement methodologies, interference dynamics, and clinical utility as surrogate tumor markers in DTC surveillance. A narrative synthesis of the relevant English-language literature was performed, focusing on key clinical studies and recent guidelines. TgAb can lead to the underestimation of Tg levels in immunometric assays, potentially masking residual disease. Trend monitoring, rather than absolute antithyroglobulin antibody values, provides superior prognostic information; declining trends indicate favorable outcomes, whereas rising trends are associated with disease persistence or recurrence. *De novo* antithyroglobulin antibody positivity does not appear to serve as an early biomarker of recurrence. In antithyroglobulin antibody–positive patients, imaging-based surveillance, particularly neck ultrasonography, remains the cornerstone of follow-up. In conclusion, TgAb act as both interferents and surrogate tumor markers in DTC surveillance, and the integrated use of antithyroglobulin antibody trends and imaging is necessary for the optimal management of antithyroglobulin antibody–positive patients.

INTRODUCTION

Differentiated thyroid cancers (DTCs) are the most common endocrine malignancies, with the majority associated with a favorable prognosis.[1] Although active surveillance and thermal ablation are emerging as alternative approaches, the standard treatment still involves lobectomy or thyroidectomy as the initial intervention, followed by radioactive iodine (RAI) administration and long-term thyroid-stimulating hormone suppression in high-risk patients.[2]

Because thyroid tissue is the sole source of thyroglobulin (Tg), its measurement serves as an essential marker for detecting persistent or recurrent disease during DTC surveillance; however, in the presence of antithyroglobulin antibodies (TgAb), Tg measurements may yield falsely low or undetectable results due to assay interference.[3]

The prevalence of TgAb positivity in DTC ranges from 10% to 25%, which is higher than that observed in the general population.[4,5] In patients achieving an excellent response after total thyroidectomy, with or without RAI therapy, TgAb levels decline over time and eventually become negative; however, the interval between the removal or reduction of the antigenic stimulus and antibody negativity may extend up to 3 years.[6] In recent years, TgAb has been recognized not only as an interferent that compromises Tg measurement but also as an independent surrogate tumor marker reflecting disease activity.[7]

Current guidelines, including the recently published 2025 American Thyroid Association guidelines, provide limited recommendations regarding the management of patients with DTC and TgAb positivity, and the optimal follow-up of this patient population remains controversial. The presence of TgAb renders serum Tg measurements unreliable and necessitates the implementation of alternative surveillance strategies, posing a major challenge for clinicians. Addressing this clinical challenge requires a comprehensive understanding of TgAb biology, measurement methodologies, and its utility as a prognostic marker. This narrative review evaluates the role of TgAb in DTC surveillance, its clinical relevance, and practical, evidence-based approaches to patient follow-up.

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A literature search was performed using the PubMed/MEDLINE and Scopus databases through December 2025. Search terms included "antithyroglobulin antibodies," "differentiated thyroid cancer," "thyroglobulin assay interference," "tumor marker," and "surveillance." Original articles, meta-analyses, and clinical guidelines published in the English language were reviewed. Reference lists of relevant articles were manually screened to identify additional publications.

OVERVIEW OF Tg AND ANTITHYROGLOBULIN ANTIBODIES

Tg is a major thyroidal protein encoded on chromosome 8q24, constituting approximately 80% of total thyroidal proteins. The Tg molecule, which serves as the precursor for the thyroid hormones T3 and T4, undergoes several posttranslational modifications. The most important of these is the iodination of tyrosine residues on Tg, which is essential for thyroid hormone synthesis. These posttranslational modifications result in substantial molecular heterogeneity of Tg, even within the same individual, and contribute to the generation of diverse TgAb targeting different epitopes of the Tg molecule. In addition, differences in TgAb profiles between patients with autoimmune thyroid disease (AITD) and healthy individuals create inherent challenges in assay standardization and result interpretation.[8]

The molecular characteristics of serum Tg may differ among various diseases. A previous study demonstrated that, in Graves' disease and subacute thyroiditis, serum Tg predominantly consists of high-molecular-weight forms, which are thought to reflect release from intact thyrocytes during active hormone synthesis or inflammation. In contrast, in DTC, Tg exhibits lower molecular weights and distinct immunoreactivity patterns, suggesting altered processing or degradation by malignant cells. These disease-specific differences in Tg composition influence antigenicity and epitope exposure, resulting in distinct TgAb responses in benign versus malignant conditions.[9]

The majority of TgAb belong to the immunoglobulin G subclass, do not fix complement, and have a half-life of approximately 10 weeks. Table 1 summarizes the wide variability in reported TgAb prevalence across different populations and thyroid diseases. Although detectable TgAb levels can be observed in up to 25% of healthy individuals using highly sensitive assays, most cases present with low-titer positivity, and the overall prevalence in the general population is typically reported to range from 10% to 15% with contemporary immunoassay methods, with higher rates observed in women and older individuals.[8,10] TgAb levels are generally higher in patients with AITD than in the general population. They may support the diagnosis of AITD, although they are less sensitive than anti-thyroid peroxidase antibodies.[11,12]

Importantly, TgAb in AITD are usually oligoclonal and target conformational epitopes. In contrast, TgAb detected in healthy individuals tend to be polyclonal and recognize more evolutionarily conserved regions of the Tg molecule. Therefore, autoantibodies associated with thyroid disease differ in both idiotype and epitope specificity.[10]

Collectively, the biological heterogeneity of Tg and the diversity of TgAb responses across thyroid diseases underpin both the analytical and clinical challenges associated with Tg and TgAb measurement. These features are particularly relevant in the follow-up of DTC, where TgAb positivity interferes with Tg assays and complicates the interpretation of disease status and biochemical surveillance.

TgAb INTERFERENCE WITH Tg MEASUREMENT

According to current guidelines, serum Tg measurement is essential for monitoring disease prognosis in patients with DTC. Because TgAb can interfere with Tg measurement, TgAb testing is also recommended with every Tg assessment.[13,14]

TgAb tests may yield discordant results across different centers and methods.[15] These discrepancies are thought to be associated with several factors, including variations in Tg and TgAb measurement methods, low antibody titers in certain individuals, and differences in Tg epitope heterogeneity. The effects of TgAb on measured Tg levels vary depending on the type of Tg assay used. TgAb tends to cause underestimation of Tg when immunometric assays (IMA) are used, whereas both underestimation and overestimation may occur with radioimmunoassay (RIA) measurements.[5]

Immunometric assay measurement in Tg testing and TgAb interference

IMA is currently the most widely used method for Tg measurement. The IMA method operates on the "sandwich principle." In this system, serum Tg first binds to a TgAb attached to a solid phase and then to a second TgAb linked to a reporter system; signal production is directly proportional to the Tg concentration.[16] The mechanism by which TgAb interferes with IMA involves TgAb binding to the Tg molecule, blocking the access of test antibodies to Tg epitopes, and consequently reducing "sandwich" formation.[17] This can result in falsely low or undetectable Tg-IMA results, potentially masking residual or recurrent disease.[18] The magnitude of interference depends on both TgAb and Tg concentrations.[19] The combination of high TgAb and low Tg poses the greatest risk for interference, as nearly all of the small amount of Tg present may be bound by TgAb. Notably, TgAb values below the test manufacturer's positivity cut-off can also cause significant interference. While low TgAb concentrations can cause severe interference, high TgAb levels may not interfere in some samples, depending on epitope specificity.[20]

TABLE 1. Prevalence of Antithyroglobulin Antibodies Among Healthy Adults and Thyroid Diseases.

Population	TgAb prevalence (%)
Healthy adults	10-27%
Hashimoto's thyroiditis	20-90%
Graves' disease	50-60%
DTC	10-25%

The wide variation in reported prevalence rates show differences in assay sensitivity, cut-off values, and study populations.
TgAb, antithyroglobulin antibody; DTC, differentiated thyroid carcinoma.

In the follow-up of patients with DTC, highly sensitive IMAs are recommended, with highly sensitive Tg IMA defined by limit of quantification values ≤ 0.2 μg/L.[6]

Radioimmunoassay measurement in Tg testing and TgAb interference

RIA is a competitive immunoassay method. In this approach, unknown Tg in serum competes with a known amount of radiolabeled Tg (125I-Tg) for binding to polyclonal Tg antibodies immobilized in the test tube; the signal is inversely proportional to the Tg concentration.[16] Because polyclonal antibodies recognize multiple epitopes, Tg can still be detected through other epitopes even when some are blocked by TgAb; therefore, RIA has been considered more resistant to TgAb interference than IMA.[19]

However, interference issues also exist with RIA. Unlike the unidirectional (underestimation) interference observed in IMA, the presence of TgAb can lead to falsely high or low results.[21] A previous study showed that Tg-RIA values were significantly higher than those obtained by liquid chromatography–mass spectrometry in 56% of TgAb-positive patients. The main disadvantages of RIA include low functional sensitivity (0.5–1.0 μg/L), lack of automation, and limited availability.[18]

Liquid chromatography–tandem mass spectrometry (LC-MS/MS) in Tg measurement

Liquid chromatography-mass spectrometry (LC-MS)/MS is becoming increasingly utilized and is not affected by *in vitro* TgAb interference. In this method, serum proteins, including Tg and TgAb, are digested with trypsin, thereby fragmenting all proteins (including TgAb and heterophile antibodies) and eliminating potential sources of interference. Specific tryptic Tg peptides are captured by immunoaffinity and subsequently measured by mass spectrometry. Tg-MS can accurately quantify Tg added to TgAb-positive sera *in vitro*.[22]

However, clinical studies of Tg-MS in TgAb-positive patients should be interpreted with caution; Tg-MS has been reported to be undetectable in 40–43% of TgAb-positive patients with structural disease.[23,24] This paradox suggests that TgAb may not only cause *in vitro* test interference but may also accelerate Tg clearance from the circulation *in vivo*. Disadvantages of LC-MS include lower functional sensitivity compared with IMA (0.5–1.0 μg/L), lack of automation and standardization, high cost, and limited availability.[25,26]

In TgAb-positive patients with undetectable highly sensitive Tg, the additional use of Tg-MS or Tg-RIA is not recommended on a routine basis and should only be considered in selected individual cases.[6]

TgAb measurement methods

Different methods are used for TgAb measurement. Automated IMAs are currently the most widely used and include chemiluminescence immunoassay, electrochemiluminescence immunoassay, and time-resolved amplified cryptate emission. These methods offer the advantages of automation, short turnaround time, and high analytical sensitivity. Older agglutination tests that report results as titers (e.g., 1:100, 1:400) are no longer recommended because of their low sensitivity.[27]

One of the most significant issues in TgAb measurement is the lack of intermethod standardization. Although all methods are standardized against the International Reference Preparation MRC 65/93, this serves only as a calibration material; there is no universally accepted reference method for TgAb measurement.[7,28] This limitation leads to wide variations in the limit of detection, functional sensitivity, and reference intervals across different TgAb assays. In one study, TgAb positivity rates ranged from 27% to 58% when different assays were applied to the same patient samples: Roche® 58%, Beckman® 41%, Siemens® Immulite® 27%, and Thermo-Brahms® 39%.[23] This indicates that a patient classified as TgAb-negative by one method may be considered positive by another.

Manufacturer-defined cut-off values are generally optimized for AITD diagnosis and may not be appropriate for detecting Tg interference in patients with DTC. Even TgAb concentrations below the manufacturer's cut-off but above the functional sensitivity, termed "borderline TgAb," can cause significant interference in Tg-IMA and should be considered positive in DTC follow-up.[29] Conversely, some high TgAb levels may not cause interference, reflecting interindividual differences in TgAb epitope specificity.[18]

TgAb AS A SURROGATE TUMOR MARKER: CLINICAL APPROACH AND TREND MONITORING

Because the reliability of serum Tg measurement is limited in TgAb-positive patients, TgAb itself is considered a surrogate tumor marker in the follow-up of DTC. Following total thyroidectomy and RAI therapy, effective elimination of thyroid antigen is expected to result in a progressive decline in TgAb levels; failure to demonstrate this decline, or the presence of rising TgAb trends, may indicate persistent or recurrent disease. Accordingly, interpreting TgAb as a surrogate marker requires a systematic, trend-based assessment integrated with clinical context and imaging findings.

Given the limited reliability of Tg measurement in TgAb-positive DTC patients, the clinical approach should be modified. Tg and TgAb measurements should be performed in the same laboratory using the same method for each patient during follow-up; method changes, which may invalidate serial comparisons, should be avoided.[7,14] TgAb trends, rather than absolute TgAb values, should be monitored; declining TgAb levels suggest remission, whereas rising levels or *de novo* TgAb positivity should raise concern for recurrence.[14,29] The threshold for imaging should be lower in TgAb-positive patients, and periodic neck ultrasonography (US) remains the cornerstone of DTC follow-up.[7,29]

TgAb trend patterns and their clinical significance

In one of the earliest systematic descriptions of TgAb dynamics, patients were classified into three classical patterns: declining trend (greater than 50% decrease from baseline), stable trend (less than 50% change), and increasing trend (greater than 50% increase).[27] This classification is currently accepted as fundamental for interpreting TgAb kinetics in clinical follow-up. However, a recent study demonstrated that up to 36% of TgAb-positive papillary thyroid carcinoma patients may exhibit non-classical patterns that

do not fit into these three categories, including persistently very high TgAb levels without structural disease and various *de novo* positivity scenarios.[30]

Approximately 75% of patients with positive TgAb levels following total thyroidectomy and RAI therapy demonstrate a declining TgAb trend. This pattern is associated with a very low-risk of recurrence and persistent disease (< 3%) and is considered a reliable indicator of an excellent treatment response.[31] In patients with a declining trend, TgAb negativity commonly occurs within 12 to 24 months, although this period may extend up to 3 years in some cases.[6] Importantly, complete elimination of the antigen source is required for TgAb levels to become negative; therefore, a declining trend can be considered indirect evidence of successful ablation, particularly in radioiodine-naïve patients.

Progressively increasing TgAb levels have been associated with a markedly increased risk of recurrence and/or persistent disease.[32,33] In a comprehensive meta-analysis published in 2020, patients with persistent or increasing TgAb trends were shown to have an approximately 10-fold higher risk of cancer persistence and recurrence [odds ratio (OR) = 9.90; 95% confidence interval (CI): 4.36–22.50] and a 15-fold higher risk of cancer mortality (OR = 15.18; 95% CI: 2.99–77) compared with patients with declining trends.[34] These findings clearly indicate that a rising TgAb trend warrants further evaluation with advanced imaging to assess for structural disease.

A stable TgAb trend represents the most complex pattern for clinical interpretation. While TgAb levels remaining stable at low levels may reflect a disease-free state, persistently stable high levels have been associated with an increased risk of recurrence (approximately 20%).[35] Therefore, in the presence of stable TgAb levels, the absolute value should also be considered, and close follow-up with periodic imaging is recommended.

Timing and threshold values in TgAb assessment

The prognostic value of TgAb trends depends on the timing of assessment. Studies have reported that TgAb changes at 6 months post-surgery have greater predictive value for recurrence than assessments at 3 months.[36] Similarly, in a retrospective cohort with a median follow-up of 7.1 years, TgAb values at 6 months were significantly associated with treatment response, with higher levels observed in patients with incomplete response compared to those with an excellent response. Notably, serum Tg levels showed no significant association with treatment response during the first year of follow-up in these TgAb-positive patients, further supporting the role of TgAb as the primary monitoring tool in this population.[37] It has been shown that decrements greater than 77.9% at 6 months and 88.6% at 2 years after radioiodine therapy are associated with a favorable prognosis.[38] These cut-off values may help guide clinical decision-making.

Comparison of TgAb levels before and after radioiodine therapy also provides prognostic information. A significant decline in TgAb levels supports a favorable treatment response, whereas stable or increasing levels raise suspicion of persistent disease.[39]

De novo TgAb positivity

De novo TgAb positivity is defined as the development of TgAb positivity during follow-up in patients who were initially TgAb-negative. *De novo* TgAb positivity was detected in approximately 5% of DTC patients.[38] When patients with persistently negative TgAb were compared with those who developed *de novo* positivity, no significant difference in recurrence was observed. Interestingly, in all patients who developed *de novo* TgAb positivity and experienced recurrence, TgAb was negative at the time of recurrence detection. TgAb became positive at a median of 2.1 years after structural recurrence was identified. These findings cast doubt on the value of *de novo* TgAb as an early biomarker.[40]

In another study, *de novo* TgAb positivity occurred in 3.3% of cases. No significant difference in structural recurrence was observed between patients with *de novo* TgAb development and those with persistently TgAb-negative status. Importantly, the majority (70%) of patients with *de novo* TgAb positivity had transient TgAb elevation, which may reflect spontaneous fluctuations related to thyroid tissue destruction following radioiodine therapy. Sustained *de novo* TgAb appearance was characterized by higher peak values compared with transient cases. Notably, in the patient with sustained *de novo* TgAb who developed structural disease, serum Tg was already detectable at the time of *de novo* TgAb appearance, supporting the continued utility of highly sensitive Tg measurement in TgAb-positive patients.[41]

These findings suggest that an aggressive diagnostic strategy is unnecessary when *de novo* TgAb is detected in the context of undetectable highly sensitive Tg. However, a progressively increasing TgAb trend warrants close follow-up. Consistently, transient *de novo* TgAb positivity following radioiodine therapy resolves spontaneously within 12 to 18 months, whereas rising *de novo* TgAb levels are strongly associated with structural recurrence.[30]

Interpretation of TgAb in the setting of AITD

In DTC arising in the background of AITD, persistently elevated TgAb levels following total thyroidectomy and radioiodine therapy are classically interpreted as a sign of residual or recurrent disease. However, in the presence of AITD, such elevations may reflect ongoing underlying autoimmunity rather than persistent antigenic stimulation. Consequently, TgAb levels may remain elevated in some patients even after complete ablation and in the absence of structural disease.[29,42]

Since attributing persistently elevated TgAb solely to recurrent disease may lead to unnecessary imaging or retreatment, serological findings should be evaluated in conjunction with the clinical context and imaging studies in patients with a history of AITD.

TgAb evaluation according to risk categories

The clinical significance of TgAb positivity varies according to the patient's risk category. In one study, 383 low-risk DTC patients were evaluated over the long-term, and none developed structural disease. TgAb positivity was observed in 4.2% of these patients during follow-up. Applying a "watch-and-wait" strategy in this population

helped avoid overtreatment. Therefore, low-risk patients may not require intensive surveillance and could be evaluated with neck US and serum Tg–TgAb measurements every 12–18 months.[43]

In intermediate-risk DTC patients, TgAb assessment plays a key role in postoperative risk stratification. It has been shown that 94% of intermediate-risk patients with stimulated Tg ≤ 2 ng/mL and negative TgAb following total thyroidectomy and radioiodine therapy achieve an excellent response and can be reclassified as low-risk.[44] However, this recategorization is not possible in the presence of TgAb positivity, and these patients require closer follow-up for structural disease.

Although the prognostic role of TgAb in high-risk DTC patients has been less extensively studied than in low- and intermediate-risk groups, available evidence suggests that TgAb positivity carries unfavorable prognostic significance in this population. In high-risk papillary thyroid carcinoma patients, the combination of pre-ablation stimulated Tg < 1 ng/mL and negative TgAb is associated with an excellent response rate of 97%; this finding indirectly suggests that TgAb positivity may negatively affect treatment response in high-risk patients.[45] Therefore, in high-risk patients with TgAb positivity or rising TgAb trends, earlier evaluation using advanced imaging modalities, particularly fluorine-18 fluorodeoxyglucose positron emission tomography/computed tomography (18F-FDG PET/CT), should be considered even in the presence of negative US findings.

IMAGING STRATEGIES IN TgAb-POSITIVE PATIENTS

In TgAb-positive patients, imaging-based surveillance is essential for follow-up because Tg measurements are unreliable. The choice and frequency of imaging may vary according to the patient's risk category and TgAb trends. Neck US is the primary imaging modality for detecting locoregional recurrence in TgAb-positive DTC patients. Current guidelines recommend neck US every 6–12 months during the initial follow-up period, with intervals extended to 12–24 months in patients demonstrating declining TgAb trends and no suspicious findings.[14] US allows detection of small cervical lymph node metastases and facilitates ultrasound-guided fine-needle aspiration of suspicious lesions.

Post-therapy I-131 whole-body scintigraphy (WBS), performed 5–7 days after RAI administration, provides valuable information on residual thyroid tissue and iodine-avid metastatic disease. However, the diagnostic WBS sensitivity for detecting recurrence during follow-up is limited, and its routine use is not recommended in low- and intermediate-risk patients with negative TgAb trends.[14] In TgAb-positive patients with rising antibody trends, post-therapy WBS following empiric RAI administration may reveal occult disease not detected by other modalities.[29]

18F-FDG PET/CT plays an important role in TgAb-positive patients with rising TgAb trends and negative conventional imaging. FDG-avid disease typically indicates more aggressive tumor biology and loss of iodine uptake capacity. In a study evaluating patients with elevated TgAb levels, negative I-131 WBS, and negative or inconclusive neck US and/or chest CT findings, 18F-FDG PET/CT demonstrated a sensitivity of 100%, specificity of 50%, and accuracy of 80% in detecting recurrent disease, although the sample size was limited and scans were not contrast-enhanced 4D sectional scans.[46] Therefore, contrast-enhanced 4D CT scans or 18F-FDG PET/CT should be considered in high-risk patients or those with persistently rising TgAb despite negative neck US. Cross-sectional imaging with 4D contrast-enhanced CT of the neck and chest may be considered when US is inconclusive or when there is clinical suspicion of mediastinal or pulmonary metastases. However, the use of iodinated contrast agents requires a minimum 4–6 week interval before subsequent radioiodine therapy.[14]

AMERICAN THYROID ASSOCIATION 2025 GUIDELINE RECOMMENDATIONS

The 2025 ATA guidelines for adult patients with DTC represent a significant update from the 2015 guidelines, introducing several key changes regarding the management of TgAb-positive patients.[45] This section summarizes the current ATA recommendations on TgAb measurement, interpretation, and surveillance strategies.

The 2025 ATA guidelines recommend that serum TgAb be measured concurrently with every Tg measurement during follow-up. They emphasize that TgAb positivity renders serum Tg measurements unreliable and necessitates alternative surveillance strategies. Importantly, the 2025 guidelines recommend measuring Tg and TgAb at 6–12 weeks postoperatively rather than 3–4 weeks as previously suggested, reflecting updated data on postoperative Tg nadir kinetics (Recommendation 30).[47]

The guidelines retain the four-category response assessment system—excellent, indeterminate, biochemically incomplete, and structurally incomplete—with refined definitions applicable to TgAb-positive patients (Table 9 of ATA 2025 Guidelines). Indeterminate response is defined as the presence of non-specific imaging findings, mildly elevated serum Tg levels, or positive but stable or declining TgAb levels in patients who have undergone total thyroidectomy with or without RAI. This definition explicitly acknowledges that declining TgAb trends, even in the presence of measurable antibodies, may reflect favorable disease status.[47]

The guidelines introduce new Tg cut-off values for patients after total thyroidectomy who do not receive radioiodine: < 2.5 ng/mL indicates an excellent response, 2.5–5 ng/mL indicates an indeterminate response, and > 5 ng/mL indicates a biochemically incomplete response. However, these thresholds are not directly applicable in the presence of TgAb interference.[47]

The 2025 guidelines formally acknowledge trending TgAb as a surrogate tumor marker in TgAb-positive patients (Recommendation 47). They also emphasize that imaging remains the primary surveillance modality when TgAb levels are positive, given the limitations of relying solely on TgAb trends for disease monitoring.

The guidelines recognize three TgAb trend patterns with distinct clinical implications:

Declining trends: Associated with favorable outcomes and may be classified as an indeterminate response.

Stable trends: Requires continued surveillance with imaging.

Rising trends: Should prompt consideration of structural disease evaluation using appropriate imaging modalities.

A clinical algorithm integrating the ATA 2025 recommendations for TgAb trend-based surveillance in TgAb-positive DTC patients is presented in Figure 1. For TgAb-positive patients, the guidelines recommend imaging-based surveillance as the cornerstone of follow-up. Neck US remains the primary imaging modality for detecting locoregional recurrence, with intervals determined by initial risk stratification and response to therapy.[45] 18F-FDG PET/CT should be considered in patients with rising TgAb trends and negative conventional imaging, particularly in those with higher-risk features or aggressive histological subtypes.[47]

The 2025 guidelines introduce a refined four-tier risk-of-recurrence stratification system—low, low-intermediate, intermediate-high, and high—replacing the previous three-tier system. This updated classification incorporates TgAb status into the overall risk assessment and emphasizes that postoperative Tg and TgAb measurements at 6–12 weeks contribute to risk restratification.[47]

A notable addition in 2025 is the formal recommendation to de-escalate surveillance in appropriately selected patients (Recommendation 48). For patients with low-risk DTC who have maintained an excellent response for 5–8 years after total thyroidectomy (with negative imaging and Tg < 0.2 ng/mL after radioiodine or < 2.5 ng/mL without radioiodine), discontinuation of routine US in favor of Tg monitoring every 1–2 years is recommended.[47]

The guidelines also introduce the concept of complete remission for low-risk DTC patients treated with total thyroidectomy, with or without radioiodine, who maintain a sustained excellent response for 10–15 years. In such cases, discontinuation of Tg and TgAb monitoring may be considered.[47]

However, these de-escalation recommendations primarily apply to TgAb-negative patients with reliable Tg measurements. For TgAb-positive patients, continued imaging-based surveillance remains essential, and de-escalation should be approached with caution.

Table 2 summarizes the major updates in the ATA 2025 guidelines compared with the ATA 2015 guidelines regarding TgAb-related recommendations.

CONCLUSION AND FUTURE PERSPECTIVES

This review demonstrates that TgAb in DTC follow-up is not only an interferent but also an independent surrogate tumor marker with prognostic value. Current evidence supports trend monitoring rather than relying on absolute TgAb values, and emphasizes the importance of using consistent measurement methods throughout follow-up as a more reliable approach for clinical decision-making.

Future priorities include accelerating international standardization efforts for TgAb measurement and establishing DTC-specific cut-off values. Additionally, the development of assays capable of determining TgAb epitope specificity may provide clinical benefit by distinguishing autoimmune thyroiditis-related TgAb from tumor-associated TgAb. Artificial intelligence algorithms could further facilitate the integration of TgAb kinetics with imaging findings and clinical parameters, contributing to individualized risk assessment.

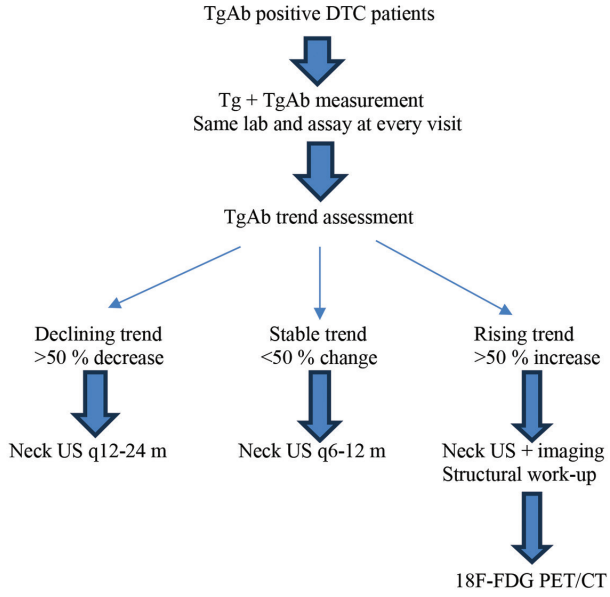

FIG. 1. Clinical algorithm for the surveillance of TgAb-positive patients with differentiated thyroid cancer based on trend monitoring and imaging strategies.

Tg, thyroglobulin; TgAb, anti-thyroglobulin antibodies; DTC, differentiated thyroid carcinoma; US, ultrasonography; 18F-FDG, 18F-fluorodeoxyglucose; PET/CT, positron emission tomography/computed tomography.

TABLE 2. Comparison of ATA 2015 and ATA 2025 Guidelines Regarding Anti-Thyroglobulin Antibodies Management.

Postoperative Tg/TgAb timing	3-4 weeks	6-12 weeks
Risk stratification	3-tier system	4-tier system
TgAb as surrogate marker	Recognized	Formally recommended (R47)
Primary surveillance in TgAb (+)	Imaging-based	Imaging-based (unchanged)
De-escalation recommendations	Limited	Formal recommendation (R48)
Complete remission	Not defined	Introduced for 10-15 year excellent responders

ATA, American Thyroid Association; R47, recommendation 47; R48, recommendation 48; Tg, thyroglobulin; TgAb, anti-thyroglobulin antibodies.

In conclusion, a multidisciplinary approach should be adopted for the follow-up of TgAb-positive DTC patients. Serological findings should be evaluated alongside structural and functional imaging, and follow-up and treatment decisions should be adapted to individual risk profiles.

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