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SCOPING REVIEW – REVISÃO DE ESCOPO

AMERICAN THYROID ASSOCIATION (ATA) 2025: KEY UPDATES IN THE TREATMENT AND LONG-TERM MANAGEMENT OF DIFFERENTIATED THYROID CANCER (DTC)

AMERICAN THYROID ASSOCIATION (ATA) 2025: DESTAQUES DA ATUALIZAÇÃO NO TRATAMENTO E MONITORAMENTO DE LONGO PRAZO DO CÂNCER DIFERENCIADO DE TIREOIDE (CDT)

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Abstract

This review summarizes the main highlights of the recent American Thyroid Association (ATA) publication on the management of adult patients with differentiated thyroid cancer (DTC). The previous version, published in 2015, has now been updated in 2025, providing new guidance on treatment, surveillance, and management of recurrence in DTC patients. The present review focuses specifically on treatment and follow-up, with emphasis on active surveillance, radioablation, surgical extent, indications for radioactive iodine therapy, the role of TSH-suppressive therapy, recurrence risk and initial reponse to treatment classifications, and strategies for long-term surveillance. The management of recurrent disease once diagnosed is beyond the scope of this review. The 2025 version introduces advances in therapeutic options for low-risk patients, a new risk classification system incorporating histopathological and

molecular features, therapeutic de-escalation strategies for low- and low-intermediate risk patients, subdivision of the intermediate-risk category, the importance of ongoing reassessment of recurrence risk during follow-up, and proposals for surveillance de-escalation in low-risk DTC. This review provides a full translation of the key ATA 2025 recommendations for adult DTC management, including figures extracted from the publication, adapted for clarity and integration into this article.

Keywords: Thyroid cancer, Thyroid carcinoma, Practice guideline, Scoping review.

Resumo

Esta revisão reúne os principais destaques da recente publicação da *American Thyroid Association* (ATA), sobre as diretrizes de manejo de pacientes adultos com câncer diferenciado de tireoide (CDT). A última versão publicada em 2015, foi recém atualizada em 2025 e traz as condutas com tratamento, monitoramento e manejo das recidivas de pacientes com CDT. A revisão aqui apresentada, foca no tratamento e monitoramento do CDT, com ênfase na vigilância ativa, radioablação, extensão de cirurgia, indicação de iodoterapia, uso da terapia supressora de TSH, risco de recorrência, classificação de resposta à terapia inicialmente instituída e manejo do monitoramento de longo prazo. Não é escopo desta revisão abordar o tratamento das recidivas uma vez diagnosticadas. A versão de 2025 mostra avanços em opções terapêuticas em pacientes de baixo risco, a nova classificação de risco baseada em critérios de histopatologia e moleculares, o de-escalonamento terapêutico para pacientes de baixo risco e risco baixo-intermediário, a subdivisão do risco intermediário, a necessidade de constantemente rever a estratificação de risco ao longo do seguimento e propostas para de-escalonamento de seguimento para CDT de baixo risco. O texto desta revisão, traz a tradução na íntegra das principais recomendações do manejo do CDT em adultos da publicação da ATA 2025, incluindo figuras extraídas da publicação, adaptadas em sua estruturação para esta revisão.

Descritores: Câncer de tireoide, Carcinoma diferenciado de tireoide, Diretrizes, Revisão de escopo.

INTRODUCTION

The management of differentiated thyroid cancer (DTC) begins with assessing the risks and benefits of initiating treatment versus opting for active surveillance or monitoring (**Figure 1**). In the era of active surveillance, the decision to treat must be carefully weighed against the potential risks and benefits of surveillance, as these factors may shift over time, both during surveillance and treatment, in the context of initial diagnosis as well as potential recurrences[1]. It is essential to emphasize that the choice between treatment and surveillance should be based on well-established clinical criteria, always taking patient preferences into account.

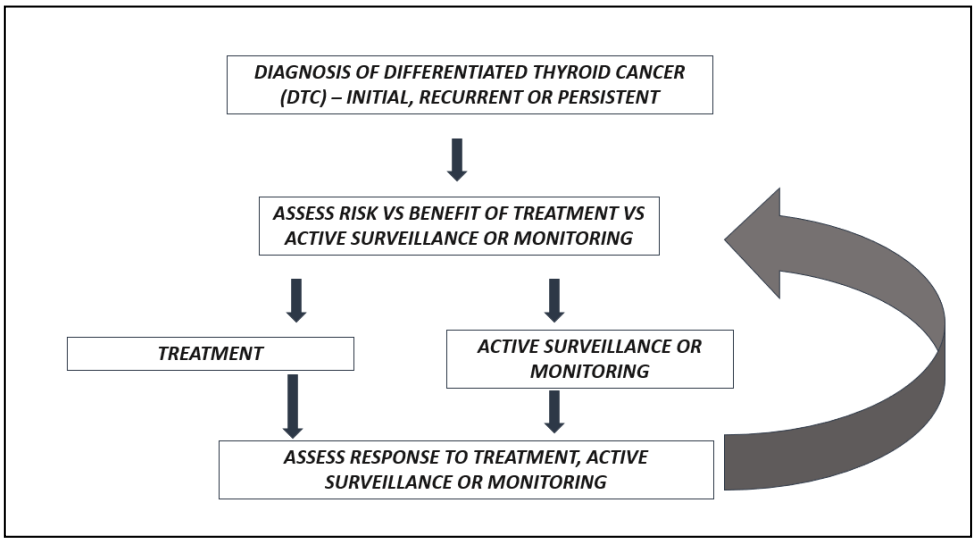

Figure 1. Continuous clinical decision-making flowchart for the clinical management of differentiated thyroid cancer (DTC).

Extracted and adapted from ATA guidelines 2025 publication[1]

In the context of the decision to treat, that is, when surgery is indicated, the primary goal is to resect the tumor and any tissue extending beyond the thyroid gland, as well as lymph nodes identified as involved either preoperatively or intraoperatively. Adequate management with complete resection of all macroscopic tumor tissue is a key factor in disease control. It is important to note that recurrences or persistent disease in the cervical region occur in approximately 74% of cases in lymph nodes, 20% in the thyroid remnant, and 6% in the trachea or other adjacent structures[2].

In addition to surgery, radioiodine therapy (RAI) and TSH-suppressive therapy may also be considered in the management of DTC. However, these modalities must be selected with careful consideration of their risks and benefits, in order to avoid imposing unnecessary therapeutic morbidity in the treatment of an indolent and low-risk tumor[1]. Therefore, it is essential to choose a treatment strategy that provides effective tumor control while minimizing morbidity, within the context of a personalized treatment plan.

Establishing risk stratification helps estimate the likelihood of recurrence in both the short and long term, while accurate staging informs disease-specific mortality estimates[1].

Another important consideration is the surgeon's experience with thyroid surgery. A surgeon who performs more than 25–50 thyroidectomies per year is considered experienced in this procedure. In general, surgeries performed by high-volume surgeons are associated with a lower risk of complications and better disease control[3,4].

PREOPERATIVE STAGING WITH LABORATORY AND IMAGING STUDIES

The use of preoperative neck ultrasound (US) to assess the extent of extrathyroidal tumor extension and the presence of cervical lymph node involvement is highly recommended. Fine-needle aspiration (FNA) of suspicious lymph nodes larger than 8–10 mm should be performed when the detection of metastasis would alter the surgical approach[1]. In contrast, thyroglobulin washout from aspirated lymph nodes should be interpreted with caution, as its diagnostic accuracy is reduced in the presence of an intact thyroid gland[1].

Lymph node metastasis is present in up to 50% of cases, even in small, intrathyroidal tumors[5]. Micrometastases (<2 mm) may occur in up to 90% of cases, depending on the diagnostic sensitivity of the method used, but unlike macrometastases, they do not appear to impact survival[6], and when confined to the central compartment, they do not seem to increase the risk of local recurrence[7].

Preoperative ultrasound detects nodal metastases in 20–31% of cases[8], and may alter the surgical strategy in approximately 20% of patients[9], especially when metastases are located in the lateral or posterior cervical compartments (levels II, III, IV, or V). For patients with more extensive extrathyroidal disease, such as suspected tracheal or esophageal invasion, large cervical nodal masses, or possible mediastinal extension, computed tomography (CT) or magnetic resonance imaging (MRI) should be combined with ultrasound to improve staging and assess resectability. Deep cervical nodes, such as retropharyngeal, parapharyngeal, or mediastinal lymph nodes, are best evaluated with CT imaging. Thus, cross-sectional imaging of the neck, chest, and upper abdomen is highly recommended during surgical planning. On the other hand, routine use of 18F-fluorodeoxyglucose PET/CT (^{18}FDG-PET/CT) is not recommended in the preoperative setting[1].

Endoscopic evaluations, such as tracheoscopy and esophagoscopy, may be considered when partial resection of these structures is anticipated based on contrast-enhanced CT or MRI findings. Preoperative laryngoscopy is strongly recommended to document recurrent laryngeal nerve function. Clinical signs such as hoarseness, hemoptysis, dysphagia, or vocal cord paresis/paralysis are highly predictive of cervical organ invasion, including gross neural or endoluminal extrathyroidal extension to the trachea or esophagus[1].

Routine measurement of preoperative thyroglobulin or anti-thyroglobulin antibodies is not recommended. A retrospective study of 422 patients with thyroid cancer found that thyroglobulin levels correlated with gland and tumor size, but not with the presence of metastasis[10]. Similarly, preoperative anti-thyroglobulin antibody levels were not associated with disease stage or overall survival[11].

Regarding preoperative genomic analysis, the 2025 ATA guidelines do not recommend routine testing, but when performed, molecular results should be interpreted alongside with clinical, radiologic, and cytopathologic data to help defining surgical extent. Some studies suggest that combined mutations in TERT and $BRAF^{V600E}$ are associated with poorer prognosis[12,13], although isolated mutations or their presence in small differentiated tumors have not consistently shown aggressive behavior[14]. A higher allelic frequency of $BRAF^{V600E}$ may indicate a more aggressive phenotype[15], especially when coexisting with other mutations[16]. RAS mutations are typically observed in follicular-pattern tumors, and are not specific to malignancy. They

may be found in follicular adenomas, noninvasive follicular thyroid neoplasms with papillary-like nuclear features (NIFTP), invasive follicular variants of papillary carcinoma, and follicular carcinoma, thus lacking predictive prognostic value when present in isolation[17]. The potential role of molecular testing to determine surgical extent may be relevant in T2N0 tumors, when the decision between lobectomy versus total thyroidectomy remains uncertain. T2 tumors with a high-risk molecular profile may benefit from total thyroidectomy, even though most T2 tumors are generally associated with low-risk molecular profiles[1].

ACTIVE SURVEILLANCE AND THERMAL ABLATION

Although there is limited evidence in the literature regarding local control rates of papillary thyroid microcarcinomas (PTMCs) treated with thermal ablation, primarily due to the novelty of the technology and the lack of long-term follow-up, it is believed that tumors suitable for ablation may also be managed with active surveillance. The choice between the two depends on clinical information and patient preference. Suitable candidates are patients with intrathyroidal tumors, with a good margin of surrounding normal thyroid tissue, located outside the posterior lobe, without contact with the trachea or the thyroid capsule, and staged as cT1a N0 M0[1].

Studies have shown that active surveillance in this group of tumors results in similar rates of disease-specific survival, distant metastasis, and recurrence compared to patients undergoing surgery[18,19]. For tumors larger than 1 cm, evidence supporting active surveillance is more limited. It is essential that, if active surveillance is chosen, the patient agrees to long-term, indefinite follow-up[1]. Active surveillance is contraindicated in cases of aggressive histology, extrathyroidal extension, lymph node metastasis, or distant metastasis[1].

One of the largest active surveillance cohort comes from Japan, where a study of 1,235 patients suggested that individuals over 60 years old are the best candidates, as their tumors exhibit lower rates of growth ≥3 mm and local or nodal progression compared to younger patients (<40 years old)[19]. A systematic review found that <10% of tumors under surveillance grew >3 mm, about 12% of patients converted to surgery, 0.1% developed distant metastasis, 2.1% had nodal metastases, and no thyroid cancer-related deaths were observed, demonstrating that active surveillance is safe in well-selected DTC patients[20]. Another systematic review found that patients undergoing active surveillance followed by delayed surgery had low disease-specific mortality, low rates of distant metastasis, and low recurrence rates. Tumor growth during surveillance was generally minimal, and conversion to surgery was most often due to patient preference. However, robust conclusions were limited due to studies design heterogeneity and quality[21].

If active surveillance is selected, ultrasound every 6 months for the first 1–2 years is the recommended imaging modality, followed by annual ultrasound thereafter[22]. Routine measurement of thyroglobulin or anti-thyroglobulin antibodies is not recommended. Surgical intervention should be indicated if any of the following occur: tumor growth ≥3 mm, biopsy-proven lymph node metastasis, distant metastasis,

extrathyroidal extension, posterior tumor growth, patient anxiety or preference, or inability to maintain appropriate follow-up[1].

Thermal ablation using radiofrequency, microwave or laser, and chemical ablation with ethanol, have been investigated as a treatment option for highly selected patients with low-risk papillary thyroid microcarcinomas. Radiofrequency ablation (RFA) may serve as an alternative for patients who decline surgery or active surveillance. Compared to lobectomy, RFA is associated with a lower incidence of hypothyroidism, but complete tumor eradication cannot be confirmed, and no tissue is available for histopathological analysis[23].

A meta-analysis showed that thermal ablation for cT1a N0 tumors resulted in complete tumor disappearance in ~96% of patients within 1 year, with no detected recurrences or lymph node metastases at 18 months of follow-up[24]. Another study involving 1,613 patients with papillary thyroid carcinoma up to 2 cm treated with RFA and followed for a median of 58.5 months, reported a tumor progression in 4.3%, recurrence in 2.6% and persistente disease in 1.7%. The mean time to tumor progression was 21.5 months. Disease-free survival varied according to tumor size (T1a *vs* T1b), number of tumors (unifocal *vs* multifocal), and the distance from the tumor to the thyroid capsule or trachea (≤2 mm *vs* >2 mm)[25]. The most recent ATA guidelines (2025) recommend caution when considering thermal ablation for T1b tumors or multifocal disease[1].

SURGICAL TREATMENT

Surgical treatment of differentiated thyroid cancer requires careful preoperative planning, particularly regarding vocal function assessment. Subjective evaluation of voice quality by the patient, physician, or family members is insufficient to ensure normal vocal cord function, and does not replace objective laryngoscopic examination. Therefore, laryngoscopy is strongly recommended in patients with pre-existing dysphonia, a history of cervical or thoracic surgery, or known thyroid cancer with gross extrathyroidal extension or bulky nodal metastases in the central or lateral neck compartments[1].

Parathyroid preservation is a critical component of thyroid surgery. Care must be taken to maintain both the glands and their vascular supply to reduce the risk of postoperative hypoparathyroidism. If a parathyroid gland is inadvertently excised or devascularized, it should be confirmed intraoperatively by frozen section and immediately autotransplanted into adjacent skeletal muscle. In cases of total thyroidectomy, central neck dissection, or completion thyroidectomy, selective or routine supplementation with calcium and vitamin D based on intraoperative or early postoperative parathyroid hormone (PTH) levels, has been shown to significantly reduce rates of symptomatic hypocalcemia and hospital readmission, compared to serial calcium monitoring alone[1].

For tumors measuring ≤2 cm without gross extrathyroidal extension or metastases (cT1N0M0), lobectomy is considered the treatment of choice, except in cases of bilateral disease or specific indications for contralateral lobe removal. For unilateral tumors between 2 and 4 cm, lobectomy remains an appropriate option,

though total thyroidectomy may be considered when postoperative radioiodine therapy is planned, when tumor features require more intensive follow-up, in the presence of suspicious contralateral nodules, or based on patient preference[1]. In patients undergoing lobectomy, it is important to provide preoperative counseling regarding the possibility of intraoperative conversion to total thyroidectomy or the need for completion thyroidectomy based on high-risk intraoperative or postoperative findings.

Total thyroidectomy is indicated in patients with tumors larger than 4 cm (cT3), any tumor with gross extrathyroidal extension (cT3b or cT4), or when lymph node (cN1) or distant metastases (cM1) are present, unless there are contraindications to the procedure. In such cases, resection should include complete removal of the primary tumor and appropriate cervical lymphadenectomy[1].

Regarding lymph node management, the 2025 American Thyroid Association (ATA) guidelines recommend against prophylactic central neck dissection in patients with small (cT1 or cT2) papillary carcinomas without clinical evidence of lymph node involvement (cN0), and for most follicular carcinomas[1]. However, prophylactic central dissection may be considered in patients with more advanced tumors (T3 or T4) or when central compartment pathology is expected to inform further therapeutic decisions. Nevertheless, the risks associated with central dissection, particularly permanent hypoparathyroidism and recurrent laryngeal nerve injury, must be carefully weighed, even in high-volume centers[1].

In patients with confirmed central compartment lymph node metastasis (cN1a), whether identified by preoperative imaging or intraoperative evaluation with or without frozen section, ipsilateral central neck dissection should be performed in combination with total thyroidectomy. For patients with lateral neck metastases (cN1b), confirmed clinically or cytologically, therapeutic dissection of cervical levels IIa, III, IV, and Vb is required[1]. In such cases, ipsilateral central neck dissection is also recommended, even if not clinically involved, as this compartment is typically considered at high risk of occult disease when ipsilateral lateral node metastases are present.

The final surgical pathology report must provide detailed information relevant to staging and prognosis. These include tumor size, margin status, the presence or absence of lymphovascular invasion, number of vessels involved, number of lymph nodes examined and those with metastatic involvement, the size of the largest metastatic lymph node, and the presence or absence of extranodal extension. Histologic subtype should be clearly defined, with particular attention to aggressive variants such as tall cell, columnar cell, *hobnail*, widely invasive follicular or oncocytic carcinomas, poorly differentiated carcinomas, high-grade well-differentiated tumors, or any areas of anaplastic transformation[1].

INITIAL RISK STRATIFICATION FOR RECURRENCE

The 2025 American Thyroid Association (ATA) guidelines recommend assessing the risk of persistent or recurrent structural disease, whether locoregional or distant, as well as disease-specific survival in patients with differentiated thyroid carcinoma. This assessment should be based on histopathological features of the tumor, the number of metastatic lymph nodes, pathological staging, postoperative imaging findings, and

serum levels of thyroglobulin and anti-thyroglobulin antibodies measured approximately three months after surgery[1].

Routine evaluation of the tumor's molecular profile is not currently recommended for estimating recurrence risk. However, when available, molecular data may be considered as an adjunct to refine risk estimation. **Figure 2** illustrates the estimated recurrence risk classification for papillary and its variants, follicular, and oncocytic thyroid carcinomas based on histopathological criteria. **Figure 3** presents recurrence risk stratification according to the molecular risk profile in differentiated thyroid cancer.

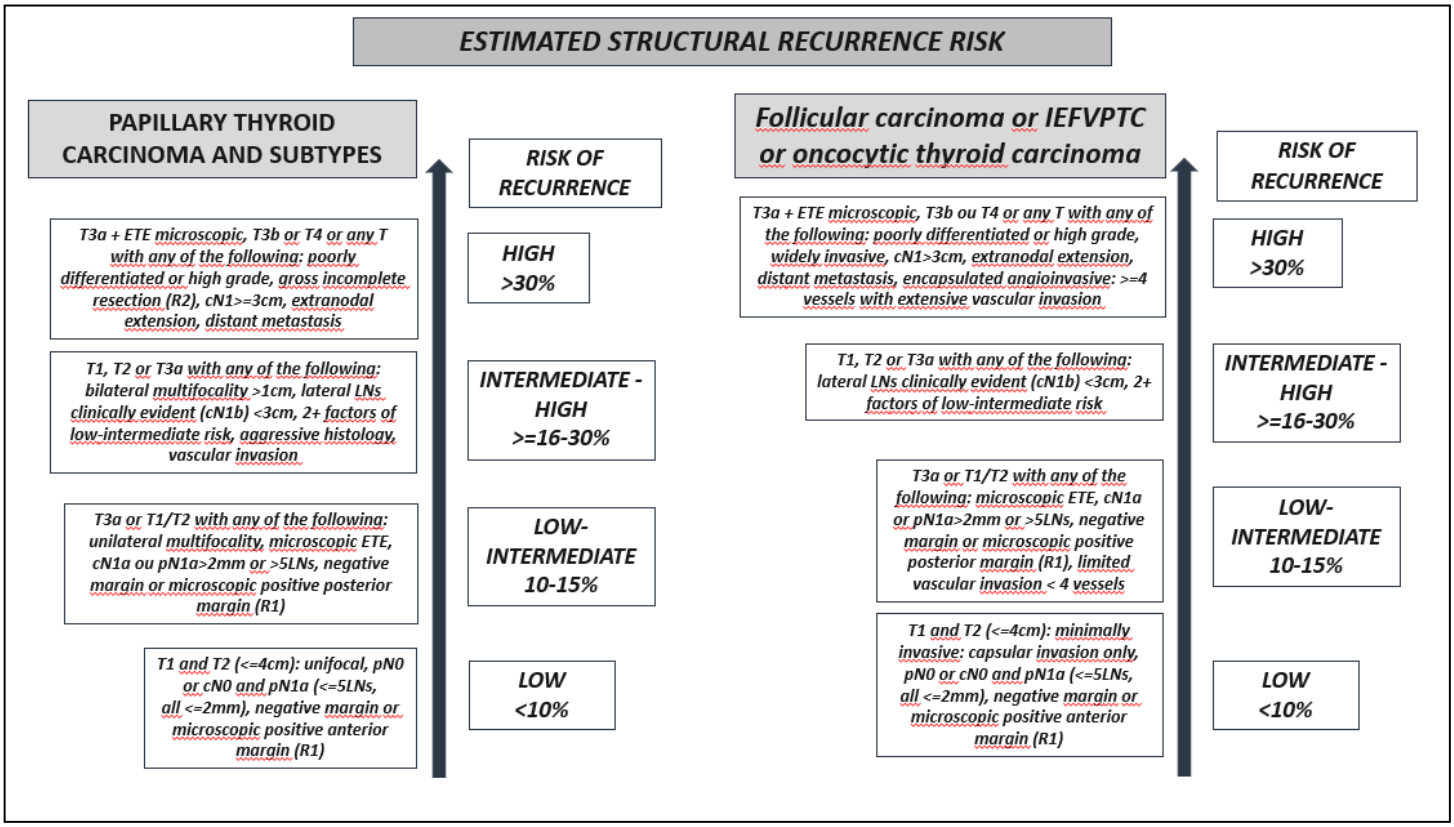

Figure 2. Estimated structural recurrence risk in thyroid cancer based on histopathological criteria.

ETE: extrathyroidal extension; LNs: lymph nodes; IEFVPTC: invasive encapsulated follicular variant of papillary thyroid carcinoma; AJCC/TNM staging system 9th edition[26]: T1 – tumor 2 cm or less in greatest dimension, limited to the thyroid; T2 – tumor more than 2 cm but not more than 4 cm in greatest dimension, limited to the thyroid; T3a – tumor more than 4 cm in greatest dimension, limited to the thyroid; T3b – tumor of any size with gross extrathyroidal extension involving strap muscles or patathyroid gland; T4a – tumor extends beyond the thyroid capsule and invades any of the following: subcutaneous soft tissues, larynx, trachea, oesophagus, recurrent laryngeal nerve or sternocleidomastoid muscle; T4b – tumor invades the prevertebral fascia, mediastinal vessels or encases the carotid artery; N1a – metastasis in level VI (central) or level VII (upper/ superior mediastinum); N1b – metastasis in other unilateral, bilateral or contralateral cervical lymph nodes like level I (submental or submandibular) / level II (upper internal jugular chain) / level III (middle internal jugular chain) / level IV (lower internal

jugular chain) / level V (cervical posterior triangle) or at retropharyngeal lymph nodes; c – clinical staging; p – pathological staging.

Extracted and adapted from ATA guidelines 2025 publication[1]

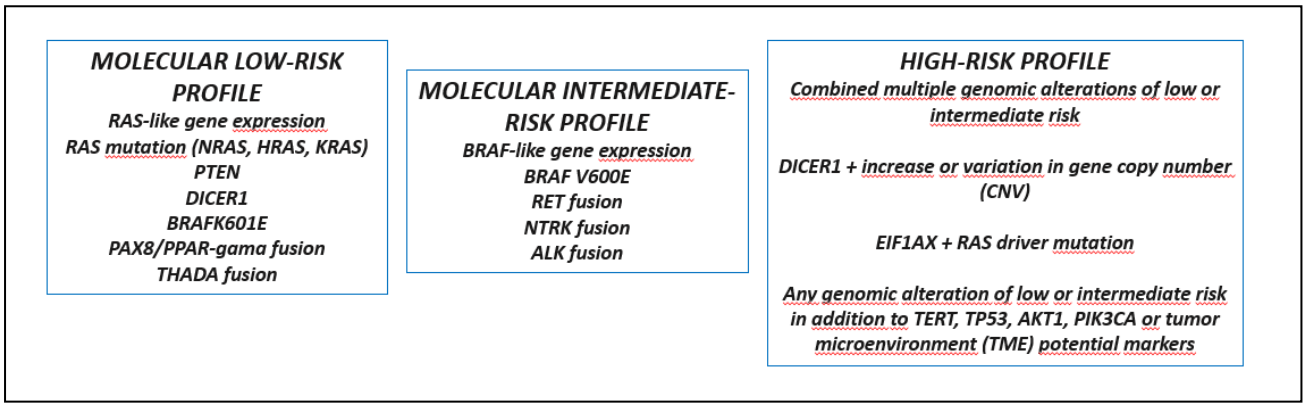

Figure 3. Molecular risk classification of thyroid cancer for estimating structural recurrence risk.

Adapted from ATA guidelines 2025 publication[1]

The ATA response to therapy system is applied to categorize the outcome of surgical treatment prior to the indication of additional therapies and follow-up, in combination with the ATA estimated recurrence risk. While recurrence risk stratification and staging provide information on structural recurrence risk and disease-specific mortality, these systems were not designed for therapeutic individualization based on treatment response. Many patients initially classified as intermediate- or high-risk according to baseline recurrence estimates are subsequently reclassified as low-risk following an excellent response to initial therapy[1].

Due to the decreased use of radioactive iodine therapy (RAI) in patients with low recurrence risk and the increased use of lobectomy, the ATA 2025 guidelines recommend the first assessment of treatment response at approximately three months after surgery. This initial evaluation provides essential information for decisions regarding the use of RAI and for tailoring its dosage. For example, a patient with multiple lymph node metastases and high recurrence risk may be considered for a lower RAI dose if, at three months after surgery, serum thyroglobulin is undetectable in the absence of anti-thyroglobulin antibodies, while on levothyroxine therapy, and with a neck ultrasound showing no residual or suspicious disease. Conversely, in the same patient, if thyroglobulin levels are detectable, further pulmonary evaluation for metastasis and higher RAI doses may be indicated, thereby altering therapeutic goals[1].

The four initial response to therapy categories were originally proposed by Tuttle et al.[27] to describe the best response to initial therapy during the first two years of follow-up[28]. Currently, however, they are applied at any point during surveillance. The categories include: **excellent response**, defined as no clinical, biochemical, or structural evidence of disease; **indeterminate response**, defined by nonspecific biochemical or structural findings that cannot be classified as benign or malignant, such as stable or declining anti-thyroglobulin antibody levels in the absence of structural disease; **biochemical incomplete response**, defined as abnormal thyroglobulin levels

or rising anti-thyroglobulin antibodies without imaging evidence of disease; and **structural incomplete response,** defined as the presence of locoregional or distant disease identified on imaging[1].

The ATA 2025 guidelines recommend serum thyroglobulin measurement 6–12 weeks after total thyroidectomy, either under levothyroxine therapy or following TSH stimulation. This assessment helps guide decisions regarding additional therapy and monitoring[1]. Measurement of thyroglobulin after lobectomy, under normal TSH levels, may be useful to rule out unexpectedly elevated values; however, reference ranges in this clinical setting remain uncertain[1]. Cervical ultrasound to assess the thyroid bed, central, and lateral compartments is strongly recommended by the ATA as part of the evaluation of response to initial therapy. If postoperative thyroglobulin levels are above those expected for an excellent response, or if anti-thyroglobulin antibodies are present, neck ultrasound or cross-sectional imaging with CT or MRI should be performed prior to RAI administration[1].

A repeat cervical ultrasound should be performed 6–12 months after completion of initial therapy, while subsequent imaging studies and timing should depend on the risk of residual or recurrent disease as well as the initial treatment response[1]. Suspicious lymph nodes or lesions <10 mm may be monitored without cytological evaluation, unless they enlarge or threaten vital structures such as vessels, nerves, the trachea, or the esophagus[1]. If cytological confirmation of recurrent or metastatic disease would alter management, lymph nodes or lesions ≥10 mm should be aspirated for cytology and thyroglobulin washout measurement[1].

In cases when thyroglobulin or anti-thyroglobulin antibody levels rise after total thyroidectomy for differentiated thyroid cancer, but cervical ultrasound reveals no structural disease, additional imaging such as CT or MRI should be considered to evaluate common metastatic sites, including the lungs and bones. In this same clinical setting, but for patients with oncocytic or poorly differentiated carcinoma, ^{18}FDG-PET/CT may also be considered[1].

USE OF RADIOIODINE THERAPY (RAI) IN THE MANAGEMENT OF DIFFERENTIATED THYROID CARCINOMA

Routine remnant ablation is not recommended after total thyroidectomy in patients with low-risk differentiated thyroid carcinoma[1]. Adjuvant RAI may be considered after total thyroidectomy in patients classified as low- to high-intermediate risk of recurrence, whereas it is strongly recommended in patients with high risk of recurrence[1]. In patients undergoing total thyroidectomy with known distant metastasis, therapeutic RAI is routinely performed[1]. The use of RAI in oncocytic carcinoma remains controversial[1]. In cases of uncertainty regarding the actual need for adjuvant RAI in this context, a diagnostic whole-body scan may be considered prior to administering an empirical dose.

For patients receiving adjuvant or empirical RAI, preparation with recombinant human TSH is preferable to levothyroxine withdrawal, particularly in those with significant comorbidities that may increase the risks associated with long-term hypothyroidism. If levothyroxine withdrawal is chosen, it should be discontinued for 3 to

4 weeks, with the aim of raising TSH to levels >30 mIU/L prior to RAI administration. In patients with known metastatic disease, preparation for therapeutic RAI may be accomplished either by levothyroxine withdrawal or by recombinant human TSH[1].

A low-iodine diet is recommended for 1 to 2 weeks before RAI ablation, adjuvant therapy, or therapeutic dosing with I-131, in order to reduce exogenous iodine exposure that could interfere with I-131 uptake by metastasis. In most cases, treatment with I-131 is performed without prior diagnostic whole-body scanning using I-123 or low-dose I-131, although such imaging may be considered at the discretion of the physician to guide therapeutic planning[1]. Post-treatment whole-body scanning should be routinely performed 2 to 10 days after ablation, adjuvant, or therapeutic RAI, to identify foci of uptake corresponding to residual disease or metastatic sites. At the time of the post-therapy scan, stimulated measurements of thyroglobulin, anti-thyroglobulin antibodies, and TSH should be obtained, with TSH ideally >30 mIU/L[1].

Adjuvant external beam radiotherapy may be considered in selected patients with high-risk disease characterized by gross extrathyroidal extension, visceral invasion, positive margins, or aggressive histological variants, particularly when surgical salvage would not be feasible in the event of recurrence[1]. The potential benefit of improved locoregional recurrence-free survival must be balanced against the absence of evidence for improved overall survival and the significant risk of toxicity. In selected cases of incomplete resection or unresectable disease, concurrent chemoradiation may be considered to enhance locoregional control, though this approach requires careful weighing of the acute and late toxicities associated with combined treatment[1].

LONG-TERM MANAGEMENT OF DIFFERENTIATED THYROID CARCINOMA AND TSH-SUPPRESSIVE THERAPY WITH LEVOTHYROXINE

The long-term management of patients with differentiated thyroid carcinoma (DTC) is guided by two main principles: monitoring for the detection of clinical recurrence and identification of tumor progression in patients with suspected or residual disease. Suppression of thyroid-stimulating hormone (TSH) with levothyroxine remains a cornerstone of therapy in this setting, as it reduces tumor stimulation and the likelihood of recurrence[1]. **Figure 4** illustrates the framework for long-term management in these patients.

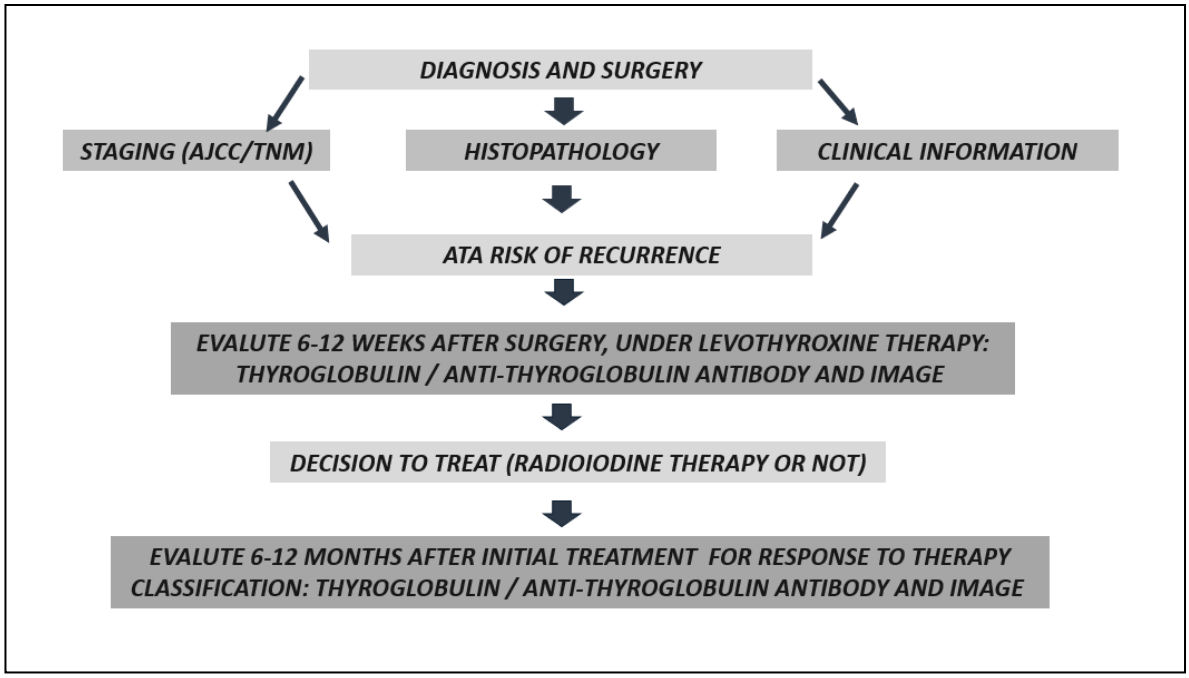

Figure 4. Framework for the management of differentiated thyroid cancer after initial therapy, aimed at guiding treatment decisions and follow-up based on a dynamic risk stratification for recurrence.

AJCC: American Joint Committee on Cancer; TNM: Tumor/ Nodes/ Metastasis[26]
Extracted and adapted from ATA guidelines 2025 publication[1]

High-specificity diagnostic tools allow the identification of patients with a minimal likelihood of recurrence, enabling the use of less aggressive treatments, thereby reducing toxicity and improving cost-effectiveness[1]. De-escalation of follow-up intensity is possible in low-risk patients several years after initial therapy, provided they maintain a persistent excellent response to treatment[1]. Conversely, patients at high risk of recurrence should undergo closer surveillance, as early detection of recurrence provides the best opportunity for an effective therapeutic response[1]. A shared decision-making model should be established with the patient, considering survival outcomes, response to therapy, short- and long-term toxicities, and the financial implications of both treatment and surveillance, as well as their sequelae.

In patients who have undergone total thyroidectomy, the most sensitive biomarker for recurrence detection is serum thyroglobulin (Tg). For this reason, Tg should be measured post-treatment and throughout follow-up in patients with differentiated thyroid carcinoma, in conjunction with anti-thyroglobulin antibody (TgAb) levels[1]. Measurement of Tg while patients are receiving levothyroxine replacement, after total thyroidectomy with or without RAI, is recommended to evaluate initial therapeutic response and to detect recurrence[1]. The first Tg measurement should be obtained approximately 3 months postoperatively, and thereafter every 6–12 months, particularly in intermediate- to high-risk patients[1]. Routine Tg measurement after lobectomy in patients on levothyroxine is generally not recommended[1].

In patients with circulating TgAb, serial trends of antibody levels, measured with the same assay, may be useful for disease monitoring. However, both immunometric and radioimmunometric Tg assays are affected by TgAb interference[1]. Therefore, in

this setting, surveillance for residual or recurrent disease should not rely exclusively on biochemical markers, but primarily on imaging studies[1]. **Figure 5** summarizes the desirable ranges of stimulated and non-stimulated Tg, along with TgAb trends and their integration with imaging findings, according to treatment modality and initial therapeutic response.

The indication, target values, and duration of TSH suppression therapy must balance potential benefits and risks. Patients at high risk of recurrence, particularly those with confirmed metastatic disease, derive the greatest benefit from maintaining subnormal TSH levels[1]. Conversely, TSH suppression is not indicated in low-risk patients or in intermediate-risk patients without biochemical or structural evidence of recurrence[1]. The risks and benefits of suppression, as well as TSH goals, should be continuously reassessed during follow-up, in accordance with dynamic risk stratification[1]. In patients with comorbidities such as osteoporosis or atrial fibrillation, TSH suppression targets should be applied cautiously, even in high-risk settings such as biochemical incomplete response to therapy and even in structural incomplete response to therapy, in order to avoid treatment-related morbidity that may outweigh the risks of tumor progression or recurrence. **Figure 5** outlines the definitions of treatment response according to the type of therapy performed, including the corresponding TSH suppression targets.

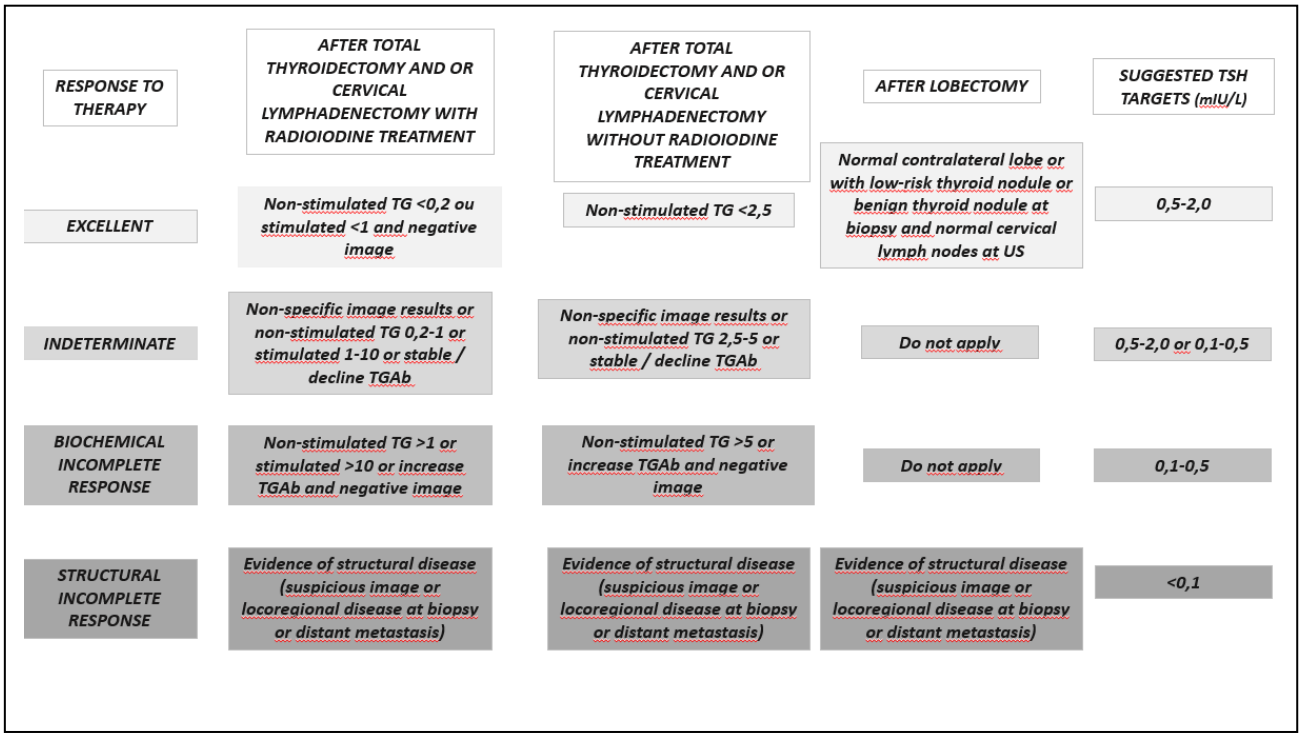

Figure 5. Definitions of therapeutic response according to the type of treatment administered and recommended TSH levels for each response to therapy category.

TG: thyroglobulin; TGAb: anti-thyroglobulin antibody; US: ultrasound; thyroglobulin values are presented in ng/mL.

Extracted and adapted from ATA guidelines 2025 publication[1]

Patients with low-risk differentiated thyroid cancer (DTC) treated with total thyroidectomy, with or without radioactive iodine therapy (RAI), and who maintain an excellent response for 5 to 8 years following initial therapy, may discontinue routine neck ultrasound[1]. In such cases, follow-up can be conducted using biochemical markers alone, assessed every 1 to 2 years. If the excellent response persists for 10 to 15 years, these patients are considered to be in complete remission and do not require further serum thyroglobulin (Tg) or anti-thyroglobulin antibody (TgAb) measurements[1].

For low-risk patients treated with lobectomy alone, if the baseline ultrasound is negative, subsequent imaging may be performed every 1 to 3 years for a period of 5 to 8 years post-treatment. Any nodules detected in the contralateral lobe should be managed according to the American Thyroid Association (ATA) guidelines for thyroid nodule evaluation. In patients treated with lobectomy whose serum thyroglobulin was measured 3 months postoperatively and was not significantly elevated, further Tg testing during follow-up is not recommended[1]. **Figure 6** outlines the recommended de-escalation strategies for monitoring patients with low-risk differentiated thyroid carcinoma who demonstrate an excellent response to initial therapy.

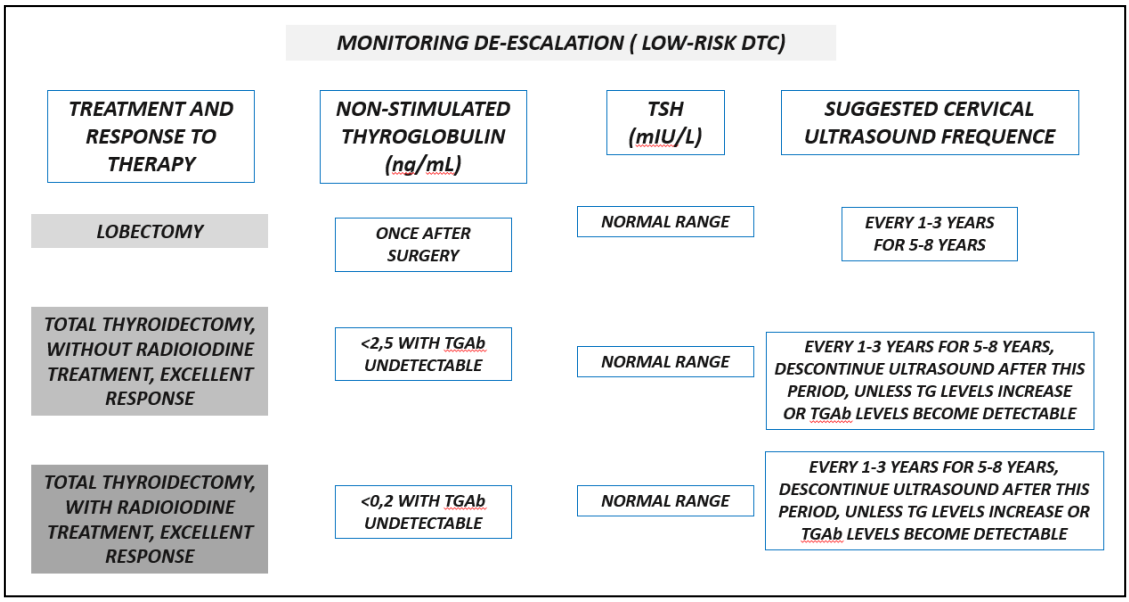

Figure 6. Recommended de-escalation strategies for surveillance in patients with low-risk differentiated thyroid carcinoma (DTC) showing an excellent response to initial therapy.

TG: thyroglobulin; TGAb: anti-thyroglobulin antibody.

Extracted and adapted from ATA guidelines 2025 publication[1]

Patients treated with lobectomy or total thyroidectomy without radioactive iodine therapy (RAI), as well as those classified as low- or low-intermediate risk of recurrence who demonstrate an excellent response to therapy, do not require diagnostic whole-body scans (DxWBS) with iodine during follow-up[1]. In contrast, patients classified as high-intermediate or high risk of recurrence may undergo DxWBS to assess iodine

avidity when there is clinical suspicion of recurrence[1]. When indicated, the diagnostic scan may be performed using either low-dose iodine-131 or iodine-123.

The use of ^{18}FDG PET/CT may be appropriate in high-risk differentiated thyroid cancer patients with elevated serum thyroglobulin levels, particularly in those with oncocytic carcinoma, aggressive histological variants, or in cases with negative imaging following a diagnostic or empiric RAI therapy dose[1]. ^{18}FDG-PET/CT may also serve as a prognostic tool in patients at high risk of disease progression or cancer-related mortality, and can be useful for evaluating the response to local or systemic treatment of invasive disease[1].

When combined with the initial recurrence risk stratification, dynamic risk assessment allows for individualized management, as the estimated risk evolves over time with continued follow-up. This approach helps guide the intensity, frequency, and type of surveillance testing[1]. **Figure 7** outlines this dynamic risk classification following initial therapy. Initial pathology, imaging, and clinical evaluation are used to estimate the risk of recurrence and inform therapeutic decisions. Subsequent assessment of treatment response leads to a revised recurrence risk estimate, which then informs long-term follow-up strategies.

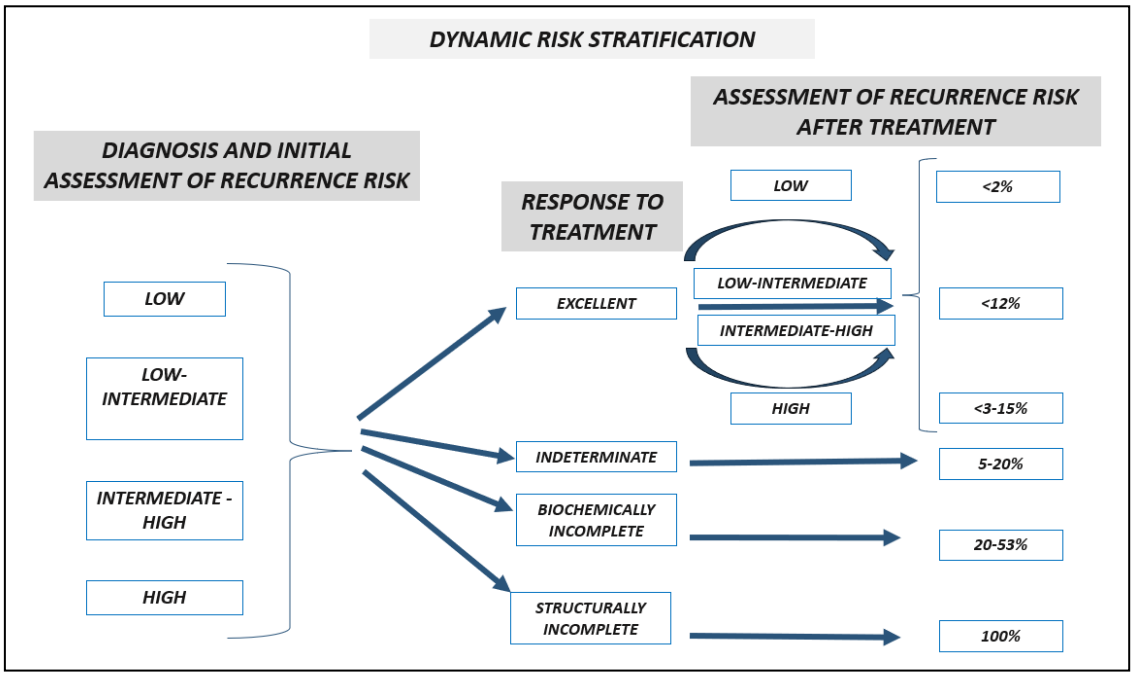

Figure 7. Dynamic risk stratification to guide ongoing long-term surveillance in patients with differentiated thyroid cancer.

Extracted and adapted from ATA guidelines 2025 publication[1]

CONCLUSION

The most recent American Thyroid Association (ATA) publication introduces important updates regarding the need for treatment and surveillance de-

escalation in patients with low-risk of recurrence, as well as the potential for active surveillance in selected low-risk tumors. Radioablation has been discussed as an alternative to active surveillance in highly selected cases; however, long-term studies are still lacking to establish its efficacy and safety in the management of papillary thyroid microcarcinoma. Furthermore, the new stratification of intermediate-risk tumors and the emphasis on dynamic risk assessment throughout follow-up, based on the patient's response to therapy, enable tailored de-escalation of monitoring, particularly in low-risk patients. These recommendations are of critical importance, as they aim to reduce treatment-related morbidity in a cancer that is generally indolent, highly curable, and increasingly overdiagnosed, which in turn contributes to overtreatment and unnecessary long-term surveillance testing and costs.

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