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Review

# What Has Changed in the 2025 American Thyroid Association Management Guidelines for Adult Patients with Differentiated Thyroid Cancer? Part 2: Postoperative Initial Treatment

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**Abstract**

American Thyroid Association (ATA) guidelines for the management of thyroid nodules and differentiated thyroid cancer (DTC) were first published in 1996 and subsequently updated in 2006, 2009, and 2015. In 2025, the ATA released a revised version focusing exclusively on DTC and excluding thyroid nodules from its scope. In our previous review, we summarized the updates regarding preoperative evaluation, diagnosis, and surgical management of DTC. In this second part of the series, we aimed to compare the 2015 and 2025 ATA guidelines in terms of initial postoperative management. The main changes are evaluated at the level of recommendations, with a particular emphasis on recurrence risk stratification, postoperative risk-adapted surveillance, adjuvant radioactive iodine (RAI) use, postoperative imaging, and radiation safety. This review provides a comprehensive comparison of the 2015 and 2025 ATA guidelines, outlining the key changes in early postoperative management of DTC and highlighting their potential impact on individualized patient care.

**Keywords:** ATA risk stratification system, differentiated thyroid cancer, papillary thyroid cancer, postoperative management, radioactive iodine therapy

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The American Thyroid Association (ATA) first issued clinical practice guidelines for the management of thyroid nodules and differentiated thyroid cancer (DTC) in 1996, with major revisions published in 2006, 2009, and 2015.[1–4]

In response to the growing body of evidence and emerging advances in diagnosis and treatment, the ATA elected to publish two distinct guideline documents. Following an extensive review of the literature, the first of these, addressing the management of DTC in adult patients, was released.[5]

This latest guideline introduces several significant changes compared with the 2015 edition. In the present study, we aimed to compare, at the level of recommendations, the differences between the 2015 and 2025 ATA guidelines regarding initial postoperative management, as a continuation of our prior review that focused on preoperative evaluation, diagnosis, and surgical management. As highlighted in our previous work, the 2015 guideline contained 101 recommendations, 31 of which were related to thyroid

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nodules and 70 to DTC,[4] whereas the most recent guideline comprises 84 recommendations exclusively dedicated to DTC.[5]

This paper represents the second part of our review series and focuses specifically on the updates related to the initial postoperative management of DTC.

## Methods

Given the expanding literature on thyroid nodules and DTC, the ATA divided the guideline development into two separate documents. The ATA President, with approval from the Board of Directors, appointed task force chairs, who subsequently formed a multidisciplinary committee. This group consisted of experts from endocrinology, endocrine and otolaryngology–head and neck surgery, nuclear medicine, pathology, medical oncology, cancer genetics, and medical informatics/clinical epidemiology. Notably, for the first time, a patient advocate participated in the process. To ensure diversity of expertise, geography, and perspective, at least one-third of the task force members were newly appointed and had not contributed to earlier ATA guidelines.

### Systematic review methods

A structured series of systematic reviews was conducted, guided by the PICO framework (Population, Interventions, Comparisons, Outcomes). The target population was patients diagnosed with DTC. Outcomes were prioritized by consensus, with survival and mortality considered primary, followed by oncologic endpoints such as metastasis, progression, and recurrence, and then clinical outcomes including quality of life, functional status, and treatment-related adverse events. Intermediate outcomes were given lower priority.

For selected key topics, such as active surveillance versus upfront surgery and the diagnostic utility of serum thyroglobulin (Tg) measurement after thyroidectomy without radioactive iodine (RAI), systematic reviews were performed by the Pacific Northwest Evidence-based Practice Center.[6,7] Searches were executed in MEDLINE, Embase and Cochrane Central, supplemented by reference screening, and restricted to English language studies. Study selection, data extraction, and risk of bias assessments were independently performed by two reviewers. The certainty of evidence was graded using a methodology adapted from the GRADE (Grading of Recommendations, Assessment, Development, and Evaluation) Working Group, accounting for bias, consistency, directness, precision, and potential publication bias. Evidence was rated as "high," "moderate," "low," or "very low" certainty, reflecting confidence in the findings. When evidence was inadequate for reliable conclusions, it was categorized as "insufficient" following the modified GRADE methodology of the American College of Physicians.[8]

For other key questions, task force members undertook independent literature searches with support from information specialists and used GRADE-based methods to evaluate study quality.

### Guideline development methods

Draft recommendations were developed within subgroups based on the systematic review findings and then refined through full-committee review. Final approval required a majority consensus of members without conflicts of interest. Study quality was evaluated using criteria derived from the U.S. Preventive Services Task Force and Cochrane Collaboration.[9,10] Each recommendation was classified as either strong or conditional.[11]

Strong recommendations were issued when benefits clearly outweighed harms with at least moderate certainty, and they were intended to apply to nearly all patients or settings. Additional factors justifying strong recommendations included minimal variability in patient values, high feasibility, acceptability, cost-effectiveness, and anticipated improvements in equity. When certainty of evidence was low, a strong recommendation required compelling justification for anticipated benefit. Conditional recommendations were used when benefits and harms were more closely balanced, when evidence certainty was limited, or when patient preferences and contextual factors might lead to different decisions.

Where evidence was insufficient but clinical consensus deemed guidance necessary, Good Practice Statements (GPS) were issued.[12] GPS function similarly to strong recommendations and represent actions considered standard of care, supported by indirect but compelling evidence. GPS issuance required the unanimous agreement of the task force.

A final literature update was conducted through July 1, 2024, with inclusion of the 2025 WHO tumor classification update as the only exception. Recommendations were revised until full consensus was achieved. Patient representatives were actively involved in all deliberations.

The final guideline was subsequently reviewed and approved by the ATA Clinical Practice Guidelines and Statements Committee and the ATA Board of Directors, and ATA members provided feedback during Fall 2024 prior to journal submission. The complete organization of recommendations is presented in the table of contents.

## 2025 RECOMMENDATIONS

### Basic principles of histopathological evaluation of thyroidectomy specimens

The basic principles for histopathological evaluation were presented in three sections in Recommendation 46 of the 2015 revision, and in three sections in Recommendation 27 of the 2025 revision.

In the first section of Recommendation 27, it is stated that, in addition to the fundamental histopathological characteristics needed for AJCC staging (such as the condition of resection margins), data that assist with risk assessment should also be included in the pathology report. These include the presence of vascular invasion and the number of invaded vessels, the number of examined and tumor-involved lymph nodes, the size of the largest metastatic focus in the lymph nodes, and the presence or absence of extranodal extension. (Good Practice Statement) This recommendation is almost the same as the 2015 edition.

In the second section, it is advised that histopathological subtypes of DTC associated with adverse outcomes (prognosis) (e.g., tall cell, columnar cell, hobnail variants of papillary thyroid carcinoma, widely invasive follicular thyroid carcinoma [FTC], oncocytic thyroid carcinoma [OTC], and high-grade follicular cell-derived non-anaplastic thyroid carcinoma) or subtypes associated with favourable prognosis (e.g., minimally invasive encapsulated follicular variant of papillary thyroid carcinoma [IEFVPTC] and minimally invasive FTC) should be identified and reported in histopathological examination (Good Practice Statement).[5]

Although the basis of the recommendation is the same as in the 2015 revision, it is noteworthy that there are differences in the subtypes listed as examples. The main reason for this is that the 2015 revision was based on the 4th edition of the World Health Organization (WHO) classification of endocrine tumors published in 2004, whereas the 2025 revision took into account the most recent edition (5$^{th}$ edition), published in 2022.

Accordingly, in the 2015 revision, the entities included in the 4$^{th}$ edition—such as poorly differentiated thyroid carcinoma and non-invasive encapsulated follicular variant papillary thyroid carcinoma—were removed. In line with the changes introduced in the 2022 classification, the following were added: widely invasive follicular thyroid carcinoma, OTC, high-grade follicular cell-derived non-anaplastic thyroid carcinoma and IEFVPTC.[13]

In the third section it is stated that, histopathological subtypes linked to familial syndromes (cribriform-morular carcinoma, which may be associated with familial adenomatous polyposis; PTEN hamartoma tumor syndrome [PHTS], which is associated with FTC or PTC) should be recognized and reported. (Good Practice Statement) This recommendation is the same as the 2015 revision.

In the 2025 revision, the discussion under the recommendation aims to strengthen standardization and international comparability by suggesting the use of standardized, structured reporting templates for pathology developed by the College of American Pathologists (CAP).[14]

### Assessment of Recurrence Risk and Initial Evaluation

In the 2025 revision, assessment of recurrence risk and initial evaluation recommendations are provided in Recommendation 28, organized into two items.

A. The 2025 ATA Risk Stratification System is advised for assessing the risk of structural persistent/recurrence (locoregional and/or distant) and survival in patients with DTC. It takes into account the tumor's histopathological characteristics, the number of cervical lymph nodes, the AJCC staging system, postoperative imaging modalities, and (where applicable) serum Tg and TgAb measurements. (Strong recommendation, moderate-quality evidence)

B. Routine postoperative molecular profiling of histological specimens is not advised. However, the 2025 ATA Risk Stratification System indicates that if such information is available, it might be utilized to further refine the recurrence risk (Conditional recommendation, low-quality evidence.[5]

In addition, the prognostic use of molecular testing was previously discussed only within a limited framework, mainly in the preoperative evaluation of nodules.

The 2025 ATA Risk Stratification System has been newly developed. This system estimates the clinical outcomes of patients with DTC (PTC, FTC/IEFVPTC, OTC) at the time of initial diagnosis and after surgery, generally within the first 3 months postoperatively. Risk prediction in this system is based not only on the initial pathology report but also on biochemical and radiological data obtained within the first few months after surgery.

In this revision, recurrence risk has been provided separately for PTC, FTC, and OTC, and classified into four categories: low, low-intermediate, high-intermediate, and high.

In the 2015 revision, mortality prediction was addressed in Recommendation 47, while recurrence and persistent disease were covered in Recommendation 48, presented in three items. In Recommendation 47, AJCC/UICC staging was recommended for all patients with DTC because of its utility in predicting disease-specific mortality and the necessity for cancer registries.[4]

In Recommendation 49, for patients with DTC treated with thyroidectomy, the 2009 ATA Initial Risk Stratification Sys-

tem was recommended, based on its usefulness in predicting the risk of recurrent and/or persistent disease (Strong recommendation, Moderate-quality evidence).

In another section, it was suggested that a modified version of the 2009 ATA Initial Risk Stratification System, incorporating additional prognostic variables not included in the original system (e.g., extent of lymph node involvement, mutation status, and/or degree of vascular invasion in FTC), may be used to further improve risk classification for DTC. Yet, the 2009 Initial Risk Stratification System's additional advantage from incorporating these particular prognostic indicators has not yet been determined (Weak recommendation, Low-quality evidence).

In the final section, although not routinely advised for initial postoperative risk stratification in DTC, the BRAF mutation status—and potentially other mutations such as TERT—was reported to have the potential to refine risk prediction when interpreted in the context of other clinicopathologic risk factors (Weak recommendation, Moderate-quality evidence).[4]

In the 2015 ATA guidelines, risk assessment was carried out using a three-tiered system (low, intermediate, high risk), based on key histopathological and clinical features such as tumor size, extrathyroidal extension, and lymph node metastasis. Although postoperative serum Tg and imaging findings were considered important for diagnosis and follow-up, they were not central to the risk classification.[4]

In both revisions, molecular testing is not routinely recommended for risk assessment; however, in the 2025 revision, it is stated that if molecular testing has been performed, it may provide additional value in risk evaluation.[4,5]

## Assessment of clinical response after surgery

In the 2015 revision, Recommendation 49 stated that the initial recurrence risk estimates should be constantly adjusted during follow-up, since the risk of recurrence and disease-specific mortality may vary over time depending on the clinical course of the disease and the response to therapy (Strong recommendation, Low-quality evidence).[4]

In the 2025 revision, this recommendation has been revised. In Recommendation 29, it is stated that ATA Response to Therapy Criteria should be used in the assessment of clinical response after surgery, and these criteria should be applied together with ATA Recurrence Risk Estimates to guide decisions regarding additional therapy or the intensity of surveillance (Strong recommendation, Moderate-quality evidence).[5]

The 2025 revision has advanced the concept of dynamic risk stratification introduced in the 2015 revision to an earlier timeframe and strengthened its integration into clinical practice. The most notable innovation is the timing of the first postoperative assessment; response categories are now recommended to be applied not only during long-term follow-up but also within the first 3 months after surgery. The scope of the response categories (excellent, indeterminate, biochemical incomplete, structural incomplete) has been expanded, and it is stated that this classification can be used at every stage of the postoperative period following tumor resection. This approach represents a critical innovation, particularly for individualizing the indications and dosing of radioactive iodine (RAI) therapy. As a result, the 2025 ATA guideline, through Recommendation 29, has shifted the assessment of treatment response to an earlier period and transformed it into a dynamic tool that guides therapeutic decisions.[5]

## Measurement of postoperative Tg levels

In the 2025 revision, Recommendation 30 provides guidance on the timing of Tg measurement after total thyroidectomy and lobectomy.

The section A states that after total thyroidectomy, a postoperative serum Tg measurement is recommended at 6–12 weeks, either during thyroid hormone therapy or after TSH stimulation. These measurements can assist in making additional decisions related to clinical management. (Strong recommendation, Low-quality evidence)

According to the Section B, after lobectomy, a single serum Tg measurement at 6–12 weeks, with normal TSH levels, may be useful to confirm the absence of unexpected increases; however, no specific cutoff value has been established for this scenario (Good Practice Statement).[5]

In the 2015 revision, Recommendation 50 addressed the prediction of postoperative disease status, with three sections related to thyroglobulin and one section related to postoperative whole-body scintigraphy.

The section A indicates that postoperative disease status (e.g., presence or absence of persistent disease) should be taken into account when deciding whether additional therapy (e.g., RAI, surgery, or other treatments) is needed. (Strong recommendation, Low-quality evidence)

According to the Section B, postoperative serum Tg (during thyroid hormone therapy or following TSH stimulation) can be used to evaluate persistent disease or residual thyroid tissue and predict disease recurrence in the future. Most patients see their lowest Tg levels 3-4 weeks after surgery. (Strong recommendation, Moderate-quality evidence)

The section C states that, the ideal cutoff value for postoperative serum Tg, or the optimal timing of its measurement (during thyroid hormone therapy or after TSH stimulation) can guide decisions regarding RAI therapy, is unknown. Therefore, no recommendation can be provided (No rec-

ommendation, Insufficient evidence).[4]

In the 2015 revision, postoperative Tg measurement was recommended, although no specific timing was provided; it was emphasized that in most patients, Tg reaches its nadir within 3–4 weeks. No recommendations were given regarding the circumstances for measurement. In contrast, the 2025 revision specifies a 6–12 week timeframe for Tg measurement. The most notable update is the inclusion of Tg measurement after lobectomy, with a single measurement at 6–12 weeks potentially revealing unexpectedly high values, although no reliable cutoff has been established for this group.

## Role of Postoperative ultrasound and other imaging modalities after primary resection (CT, MRI, and 18FDG-PET-CT)

The 2025 revision, in Recommendation 31, provides guidance on postoperative imaging in seven sections. Section A states that for assessing the thyroid bed as well as the central and lateral cervical lymph node compartments, ultrasonography is the preferred modality for follow-up in most DTC patients (Strong recommendation, Moderate-quality evidence).

Section B recommends performing cervical ultrasonography and/or cross-sectional imaging before RAI therapy if the postoperative serum Tg exceeds the excellent response range or if TgAb is present (Good Practice Statement).

Section C advises performing cervical ultrasonography within 6–12 months after completion of initial therapy to evaluate the thyroid bed and cervical lymph node compartments; further timing and frequency should be determined based on residual/recurrent disease risk and response to therapy (Good Practice Statement).

Section D notes that small (<8–10 mm) suspicious lymph nodes or lesions can be monitored without fine-needle aspiration (FNA) if they don't exhibit growth or pose a threat to critical structures (recurrent laryngeal nerve, trachea, esophagus, or major vessels) (Conditional recommendation, Low-quality evidence).

Section E recommends FNA with Tg measurement in needle washout when suspicious lymph nodes or lesions are ≥8–10 mm and when cytologic confirmation would influence treatment decisions (Good Practice Statement).

Section F suggests additional cross-sectional imaging to evaluate common metastatic sites (lung, bone) if Tg or TgAb rises after total thyroidectomy but cervical ultrasonography shows no or minimal structural disease (Good Practice Statement).

Finally, Section G indicates that in cases of OTC or poorly differentiated thyroid carcinoma (PDTC), 18FDG-PET/CT may be considered when Tg or TgAb rises postoperatively, yet cervical ultrasonography shows no or minimal structural disease (Conditional recommendation, Low-quality evidence).[5]

In the 2025 revision, postoperative imaging recommendations are provided in Recommendation 31, organized into seven items. In comparison, the 2015 ATA guidelines addressed postoperative imaging in Recommendations 65, 68, and 69. The 2025 revision emphasizes that ultrasonography (US) is the preferred imaging modality for follow-up in most patients with DTC. Many of the US-related recommendations in the 2025 revision align with the 2015 guidelines, including performing US after initial therapy, defining follow-up intervals, performing biopsies for suspicious lymph nodes >8–10 mm, and measuring thyroglobulin in needle washouts.

The 2025 revision clarifies follow-up of suspicious lymph nodes or lesions with a short-axis diameter <8–10 mm, stating that these can be monitored without FNA unless they show growth or threaten vital structures. A new recommendation in 2025 advises performing cervical US and/or cross-sectional imaging before RAI therapy if the postoperative serum Tg exceeds the excellent response range or if TgAb is present.

Regarding cross-sectional imaging, the 2015 revision's Recommendation 69 included three detailed points. Section A recommends contrast-enhanced cross-sectional imaging (CT or MRI) of the neck and upper thorax in cases where (i) US cannot fully delineate extensive recurrent lymph node disease, (ii) invasive recurrent disease may require complete evaluation of aerodigestive tract invasion, or (iii) US may not adequately visualize cervical lymph node disease (e.g., high Tg with negative neck US) (Strong recommendation, Moderate-quality evidence). Section B advises considering contrast-free chest CT (for lung parenchyma) or contrast-enhanced chest CT (including mediastinum) in high-risk DTC patients with high serum Tg (generally >10 ng/mL) or rising Tg antibodies, regardless of negative RAI imaging (Strong recommendation, Moderate-quality evidence). Section C states that in high-risk DTC patients with elevated serum Tg (generally >10 ng/mL), negative neck and chest imaging, and symptoms related to other organs—or in patients preparing for TSH-stimulated RAI therapy and at risk of tumor swelling complications—imaging of other organs (including brain MRI, skeletal MRI, and/or abdominal CT or MRI) should be considered (Strong recommendation, Low-quality evidence).[4]

In the 2025 revision, cross-sectional imaging is summarized in two items, with Section B already discussed in the previous ultrasonography-related paragraph. Section F states that after total thyroidectomy for DTC, if Tg (or TgAb) levels

rise but cervical ultrasonography shows no structural disease or only minimal tumor burden, additional cross-sectional imaging is recommended to assess common metastatic sites such as the lungs and bones.

In the 2015 ATA guidelines, the use of 18FDG-PET was addressed in two items under Recommendation 68, which is summarized in a single item in Recommendation 31 of the 2025 revision. In the 2015 revision, Section A recommended considering 18FDG-PET scanning in high-risk DTC patients with elevated serum Tg (generally >10 ng/mL) and negative RAI imaging (Strong recommendation, Moderate-quality evidence). Section B further stated that 18FDG-PET may also be considered (i) as part of initial staging for poorly differentiated thyroid cancers and invasive Hurthle cell carcinoma, especially when other disease findings are present on imaging or serum Tg levels are high, (ii) as a prognostic tool to detect lesions and patients at highest risk of rapid disease progression and disease-specific mortality in metastatic cases, and (iii) for assessing treatment response following systemic or local therapy of metastatic or locally invasive disease.[4]

In the 2025 revision, it is recommended that in cases of OTC and poorly differentiated thyroid carcinoma (PDTC), 18FDG-PET/CT may be considered when Tg (or TgAb) levels rise after total thyroidectomy, even if cervical ultrasonography shows no structural disease or only minimal tumor burden.[5]

## Radioactive iodine therapy after thyroidectomy in the primary Treatment of DTC

In the 2015 revision, RAI recommendations were based on the 2015 risk classification. In contrast, the 2025 revision aligns RAI recommendations with the newly developed 2025 ATA Risk Stratification System. The 2025 RAI recommendations have also been adapted from the Martinique guidelines.[15]

## Key definitions related to RAI therapy

Remnant Ablation: The elimination of residual benign thyroid tissue in the thyroid bed to facilitate follow-up of the disease.

Adjuvant Therapy: The administration of additional RAI to decrease the risk of recurrence.

Treatment of Known Disease: The administration of RAI to treat areas of known residual or metastatic disease.

## RAI therapy after total thyroidectomy According to 2025 ATA risk stratification

For ATA low-risk DTC patients, routine remnant ablation after total thyroidectomy is not recommended (Strong recommendation, High-quality evidence).

For patients with low-intermediate or intermediate-high risk DTC, adjuvant RAI therapy after total thyroidectomy may be considered to reduce the risk of recurrence (Conditional recommendation, Low-quality evidence).

For ATA high-risk DTC patients, adjuvant RAI therapy after total thyroidectomy is routinely recommended (Strong recommendation, Moderate-quality evidence).

In patients diagnosed with DTC who have distant metastases, RAI therapy after total thyroidectomy is routinely recommended (Strong recommendation, Moderate-quality evidence).[5]

In the 2015 revision, RAI recommendations were provided in five items.

RAI Therapy after Thyroidectomy According to the 2015 ATA Guidelines (Recommendation 51, details in Table 14)

In ATA low-risk DTC patients, routine RAI remnant ablation after thyroidectomy is not recommended. Individual patient factors that may affect recurrence risk, follow-up outcomes, and patient preferences should be considered in the decision-making process (Weak recommendation, Low-quality evidence).

For patients with unifocal papillary microcarcinoma, in the absence of other adverse features, routine RAI remnant ablation after lobectomy or total thyroidectomy is not recommended (Strong recommendation, Moderate-quality evidence).

For patients with multifocal papillary microcarcinoma, in the absence of other adverse features, routine RAI remnant ablation after thyroidectomy is not recommended. Individual patient factors that could influence recurrence risk, follow-up outcomes, and patient preferences should be taken into account in the RAI decision-making process (Weak recommendation, Low-quality evidence).

For ATA intermediate-risk DTC patients, adjuvant RAI therapy after total thyroidectomy may be considered (Weak recommendation, Low-quality evidence).

For ATA high-risk DTC patients, adjuvant RAI therapy after total thyroidectomy is routinely recommended (Strong recommendation, Moderate-quality evidence).[4]

In the 2015 revision, RAI therapy was addressed in Recommendation 51, which included five items, whereas in the 2025 revision, RAI therapy is provided in Recommendation 32, summarized in four items.

In the 2015 revision, routine RAI remnant ablation after thyroidectomy was not recommended for ATA low-risk DTC patients. In addition, the recommendation emphasized that individual patient factors that could influence

recurrence risk, follow-up outcomes, and patient preferences should be considered in the RAI decision-making process (Weak recommendation, Low-quality evidence). Furthermore, two other items addressed patients with unifocal or multifocal papillary microcarcinoma: in the absence of other adverse features, routine RAI remnant ablation after thyroidectomy was not recommended. It is noteworthy that the additional caution about individual patient factors was included only for multifocal papillary microcarcinoma, not for unifocal cases. The recommendation for low-risk and multifocal papillary microcarcinoma is based on weak recommendation and low-quality evidence, whereas for unifocal papillary microcarcinoma it is a strong recommendation supported by moderate-quality evidence.

In the 2025 revision, routine remnant ablation after total thyroidectomy is also not recommended for ATA low-risk DTC patients. However, the recommendation level is strong, supported by high-quality evidence.

For intermediate-risk DTC patients, the 2015 revision suggested that adjuvant RAI therapy may be considered after total thyroidectomy (Weak recommendation, Low-quality evidence). In the 2025 revision, the intermediate-risk group has been subdivided into "low-intermediate" and "intermediate-high" risk categories. In both subgroups, RAI may be considered as adjuvant therapy, with a conditional recommendation based on low-quality evidence.

For high-risk DTC patients, routine adjuvant RAI therapy after total thyroidectomy is recommended in both 2015 and 2025 revisions, with a strong recommendation supported by moderate-quality evidence.

A new recommendation added in the 2025 revision is that for patients with distant metastases at diagnosis, routine RAI therapy after total thyroidectomy is recommended.

## RAI therapy in oncocytic thyroid carcinoma

In the 2025 revision, Recommendation 32 states that, due to limited outcome data in OTC, no definitive recommendation can be made about RAI therapy. If RAI is not applied empirically, diagnostic whole-body scintigraphy (WBS) may be considered to assess iodine avidity (Conditional recommendation, Very low-quality evidence).[5]

In the 2015 revision, no separate recommendation existed for OTC (Hurthle cell/oncocytic thyroid carcinoma). In the 2025 revision, an independent recommendation for OTC has been introduced. Although no definitive recommendation can be made, this guidance effectively removes routine RAI use in OTC and emphasizes individualized decision-making.

## Preparation for RAI Therapy

The 2025 revision provides recommendations for preparing patients for RAI therapy in Recommendation 34.

Section A states that for DTC patients scheduled for RAI remnant ablation or adjuvant therapy, rhTSH stimulation is preferred over thyroid hormone withdrawal for preparation (Strong recommendation, High-quality evidence).

Section B recommends considering rhTSH stimulation in DTC patients of any risk level who have serious comorbidities that make thyroid hormone withdrawal contraindicated (Good Practice Statement).

Section C notes that if thyroid hormone withdrawal is planned before RAI therapy or diagnostic testing, LT4 should be discontinued for at least 3–4 weeks. If LT4 withdrawal will exceed four weeks, initial replacement with liothyronine (LT3) should be considered, which must be discontinued at least 2 weeks before RAI. TSH levels should be checked prior to radioisotope administration (Good Practice Statement).

Section D recommends a TSH target >30 mIU/L for preparation prior to RAI therapy or diagnostic testing (Good Practice Statement).

Section E states that in DTC patients with known distant metastases, preparation can involve either LT4 withdrawal or rhTSH stimulation (Conditional recommendation, Low-quality evidence).[5]

In the 2015 revision, preparation for RAI therapy through thyroid hormone withdrawal was addressed in Recommendation 53 (two items), and rhTSH stimulation was addressed in Recommendation 54.

Section A states that if thyroid hormone withdrawal is planned prior to RAI therapy or diagnostic testing, LT4 should be discontinued for 3–4 weeks. If LT4 withdrawal is planned for 4 weeks or longer, liothyronine (LT3) may be used during the initial weeks, and LT3 must be discontinued at least 2 weeks before RAI. Serum TSH should be measured prior to radioisotope administration to assess the degree of TSH elevation (Strong recommendation, Moderate-quality evidence).

Section B notes that a TSH target >30 mIU/L is generally adopted for preparation before RAI therapy or diagnostic testing. However, the optimal TSH level associated with long-term outcomes remains uncertain (Weak recommendation, Low-quality evidence).[4]

Recommendation 54 – rhTSH Preparation for RAI Therapy (2015 ATA Guidelines): Section A states that rhTSH stimulation is a suitable alternative to thyroid hormone withdrawal for patients scheduled for RAI remnant ablation or adjuvant therapy, in ATA low- and intermediate-risk DTC patients

without extensive lymph node involvement (i.e., T1–T3, N0/Nx/N1a, M0). This recommendation is supported by multiple consistent observations showing superior short-term quality of life, no reduction in ablation efficacy, and no significant difference in long-term outcomes (Strong recommendation, Moderate-quality evidence).

Section B notes that rhTSH stimulation may be taken into consideration as an alternative to thyroid hormone withdrawal before adjuvant RAI therapy in ATA intermediate-risk DTC patients with widespread lymph node disease (clinically numerous LNs) but no distant metastases (Weak recommendation, Low-quality evidence).

Section C states that in ATA high-risk DTC patients, who have higher disease-related mortality and morbidity risks, more controlled long-term outcome data are needed before rhTSH preparation can be recommended for adjuvant RAI therapy (No recommendation, Insufficient evidence).

According to Section D, rhTSH preparation should be considered for DTC patients of any risk level who have serious comorbidities that might make thyroid hormone withdrawal impossible. The inability to produce a sufficient endogenous TSH response following thyroid hormone withdrawal or serious physical or mental health issues that could rapidly worsen with hypothyroidism and cause serious side effects are examples of significant comorbidities (Strong recommendation, Low-quality evidence.)

In the 2015 revision, Recommendation 53, Section A, which addresses LT4 withdrawal, and Section B, which sets the TSH target, are similarly included in the 2025 revision. In Recommendation 54, Sections A and B propose rhTSH stimulation as an alternative to thyroid hormone withdrawal in low- and intermediate-risk DTC patients. However, no recommendation regarding rhTSH use was provided for high-risk DTC patients. Additionally, Section D of Recommendation 54 states that in DTC patients of any risk level who have comorbidities that could cause serious complications if thyroid hormone withdrawal is performed, rhTSH should be considered for preparation prior to RAI therapy.[4]

In the 2025 ATA guideline, Recommendation 34, Section A, clearly states that rhTSH stimulation should be preferred over LT4 withdrawal in DTC patients prior to RAI therapy (Strong recommendation, High-quality evidence). Notably, the 2025 revision does not differentiate preparation strategies based on risk category. It emphasizes that TSH must be measured and a target of >30 mIU/L should be achieved.

In addition to the 2015 guideline, the 2025 revision introduces a recommendation for DTC patients with distant metastases, stating that either LT4 withdrawal or rhTSH stimulation may be used for preparation (Conditional recommendation, Low-quality evidence).[5]

## Low-Iodine Diet before RAI Therapy

In patients scheduled for RAI remnant ablation or therapy, a low-iodine diet should be implemented for approximately 1–2 weeks prior to treatment (Good Practice Statement).

In the 2015 revision, Recommendation 57 regarding the implementation of a low-iodine diet has remained largely unchanged in the 2025 revision.

Diagnostic Radioactive Iodine Whole-Body Scan (WBS): Timing and Indications

In the 2025 revision, Recommendation 36 addresses diagnostic RAI WBS. It states that in patients scheduled for RAI therapy after total thyroidectomy, a diagnostic 123I or low-dose 131I WBS may be considered before the therapeutic administration (ablation, adjuvant, or treatment purposes) to guide treatment schedule (Conditional recommendation, Low-quality evidence).

In the 2015 ATA guideline, diagnostic WBS was addressed in Recommendation 50, Section D. This recommendation states that postoperative diagnostic RAI WBS may be helpful in situations where the surgical report or neck ultrasonography cannot reliably assess the extent of thyroid remnant or residual illness, and where the results may change treatment decisions or the RAI activity. Simultaneous single-photon emission computed tomography (SPECT/CT) can improve the localization and identification of uptake foci. The therapeutic activity should ideally be provided within 72 hours following the diagnostic scan, which should use either low-dose 131I (1–3 mCi) or 123I (1.5–3 mCi). (Weak recommendation, Low-quality evidence).

In the 2015 revision, routine use of diagnostic WBS was not recommended, although it was noted to be potentially useful in selected cases. In the 2025 revision, it is suggested that diagnostic WBS may be beneficial if performed prior to RAI treatment planning.

## Post-therapy radioactive ıodine whole-body scan (WBS) and SPECT/CT

In the 2025 revision, Recommendation 37 states that post-therapy scans should be conducted after following RAI treatment (Strong recommendation, Moderate-quality evidence).

In the 2025 revision, Recommendation 38 states that single-photon emission computed tomography (SPECT/CT) may be performed in conjunction with diagnostic or post-therapy WBS if available (Conditional recommendation, Low-certainty evidence).

In order to document RAI uptake in any structural disease and to inform disease staging, post-treatment WBS (with or without SPECT/CT) is advised following RAI remnant abla-

tion or therapy, according to Recommendation 58 in the 2015 revision (Strong recommendation, Low-quality evidence).

In the 2015 revision, a single recommendation (Recommendation 58) addressed post-therapy WBS, stating that it could be performed with or without SPECT/CT. The 2025 revision combines these into a single recommendation, suggesting that if available, WBS should be performed in conjunction with SPECT/CT.

## Radiation safety and risks for patients

Before starting RAI preparation, patients should be given both verbal and written instructions to minimize radiation exposure to family members and the public. These instructions should comply with local regulations in the country where the treatment is performed (e.g., Nuclear Regulatory Commission guidelines in the United States) (Good Practice Statement).

In the 2015 ATA guideline, there was no separate recommendation regarding radiation safety education.[4]

In the 2025 ATA guideline, it is recommended that patients be informed with both verbal and written instructions before starting RAI preparation, and that this education comply with the regulatory guidelines of the country where the treatment is performed. This approach is stated as a Good Practice Statement.[5]

## How to Counsel Patients on RAI-Related Salivary Gland and Lacrimal Duct Side Effects, and How to Reduce Risks?

This subject is explained under the recommendation 40 as four items.

A. Patients should be informed that RAI therapy may increase the risk of secondary malignancy, lacrimal duct stenosis, and acute and chronic salivary gland morbidity (Good Practice Statement).

B. General measures, such as hydration, are recommended to prevent salivary gland side effects after RAI (Good Practice Statement).

C. Patients with xerostomia have an increased risk of dental caries; therefore, they are advised to consult their dentist for preventive strategies (Good Practice Statement).

D. Nasolacrimal duct obstruction should be considered to be treated surgically since it can cause excessive tearing (epiphora) and increased susceptibility to infection (Good Practice Statement).[4]

In the 2015 revision, Recommendation 83 did not provide guidance on routine preventive measures for salivary gland injury after RAI due to insufficient evidence.

The 2025 ATA guideline, however, modified this approach compared to Recommendation 83 in the previous guideline. Recommendation 40 in the 2025 revision states that patients should be counseled about the potential acute and chronic salivary gland morbidity, lacrimal duct stenosis, and secondary malignancy risks associated with RAI therapy (Section A). Section B specifically recommends general preventive measures, such as hydration, to protect the salivary glands.[5]

In the 2025 revision, the recommendations regarding patients with xerostomia and nasolacrimal duct obstruction were similar to Recommendations 83 and 84 in the 2015 revision.

## How to counsel patients on the risk of second primary malignancy (SPM) After RAI therapy

In the 2025 revision, Recommendation 41 states that patients who receive RAI treatment for DTC should be made aware of their risk of developing a second primary malignancy (SPM). No further health screening is advised because the absolute risk increase associated with RAI seems to be minimal. (Good Practice Statement).[5]

In the 2015 revision, Recommendation 86 stated that patients should be informed about the possibility of developing a second primary malignancy (SPM. RAI-related risk increases are, nevertheless, thought to be minimal, and it is not sufficient to justify additional screening beyond age-appropriate general population health examinations.[4]

The counseling and screening recommendations regarding the risk of secondary malignancy after RAI in the 2025 revision are similar to those in the 2015 revision.

## Other Tests to perform in patients receiving RAI therapy

In the 2025 revision, Recommendation 42 states that in patients who will receive therapeutic RAI, baseline evaluations should include a complete blood count and assessment of kidney function (Good Practice Statement).[5]

Also in the 2015 revision, it was recommended that patients receiving therapeutic doses of RAI should have a baseline complete blood count and assessment of kidney function (Weak recommendation, Low-quality evidence).[4]

The 2025 revision Recommendation 43 addresses counselling patients about RAI therapy, pregnancy, breastfeeding, and gonadal function.

A. In women of reproductive age, a negative pregnancy test should be confirmed before RAI therapy, and pregnancy should be avoided for at least 6 months after treatment (Good Practice Statement).

B. RAI should not be administered to breastfeeding women. Based on the clinical situation, treatment should be postponed until at least 3 months after cessation of breastfeeding or milk expression. In women with a recent history of breastfeeding, diagnostic 123I scanning may be considered to evaluate potential breast involvement (Good Practice Statement).

C. Male patients who have received a cumulative RAI dose exceeding 14.8 GBq (400 mCi) should be informed about the potential risk of infertility (Good Practice Statement).

D. Women should be informed that RAI therapy has not been shown to have a long-term adverse effect on fertility (Good Practice Statement).

The 2015 ATA recommendations on RAI, pregnancy, breastfeeding, and gonadal function were as follows:

Recommendation 88: Pregnancy should be avoided for 6-12 months following treatment, and women of reproductive age undergoing RAI therapy should have a negative pregnancy test before beginning treatment.

Recommendation 89: RAI should not be administered to breastfeeding women. Treatment might be delayed until the mother has stopped nursing or expressing milk for at least 3 months, depending on the clinical circumstances. To assess possible breast involvement in women who have recently breastfed, a diagnostic 123I or low-dose 131I scan may be taken into consideration.

Recommendation 90: Counseling regarding the possible risk of infertility should be given to male patients who have received cumulative RAI doses more than 400 mCi.[4]

In the 2025 revision, Recommendation 43 regarding RAI therapy and reproductive considerations largely mirrors the 2015 recommendations 88–90. Key points include: women of reproductive age should have a negative pregnancy test before RAI and avoid pregnancy for at least 6 months (revised from 6–12 months in 2015), breastfeeding women should not receive RAI, and men receiving a cumulative dose >400 mCi should be counselled regarding potential infertility. Additionally, the 2025 update adds that RAI has not been shown to have long-term adverse effects on female fertility.

## The role of radiotherapy (alone or in combination with chemotherapy) in patients with differentiated thyroid cancer (DTC)

Regarding the role of radiotherapy in DTC, Recommendation 44 in the 2025 revision provides two points:

A. Adjuvant external beam radiotherapy (EBRT) may be considered in patients with high-risk features for locoregional disease progression (e.g., aggressive histologic subtype, gross extrathyroidal extension, positive surgical margins, visceral or soft tissue invasion), particularly when anticipated progression is not amenable to salvage surgery. EBRT may improve locoregional recurrence-free survival, though evidence for improved overall survival is lacking, and significant toxicity risks must be considered (Conditional recommendation, low-level evidence).

B. In patients with macroscopic residual disease or locally advanced, unresectable DTC, EBRT—either alone or combined with chemotherapy—may improve locoregional control, but this approach may also cause acute and long-term treatment-related toxicity (Conditional recommendation, low-level evidence).

In the 2015 revision, Recommendation 60 states that in patients with DTC, routine adjuvant EBRT to the neck after initial complete surgical resection has no established role (Strong recommendation, Low-quality evidence).

Recommendation 61 indicates that in DTC patients, routine systemic adjuvant therapy beyond TSH-suppressive therapy with RAI and/or LT4 has no established role (Strong recommendation, Low-quality evidence).[4]

In the 2015 revision, it was stated that adjuvant radiotherapy and chemotherapy have no established benefit after initial surgical treatment. In the 2025 revision, this recommendation is no longer included; instead, adjuvant EBRT is limited to selected patients with high-risk features in whom salvage surgery is not feasible. The guideline frames EBRT use by balancing potential benefits (local-regional control) against harms (toxicity and lack of survival benefit). Additionally, it notes that in selected cases, EBRT can be administered concurrently with chemotherapy.[4,5]

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