Update in Papillary Thyroid Cancer

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KEYWORDS

• Differentiated thyroid cancer • Active surveillance • Thyroid lobectomy
• Total thyroidectomy • Serum thyroglobulin • Thyroid cancer surveillance
• TSH suppression

KEY POINTS

- Active surveillance of thyroid cancer is considered in patients age >60 with a nodule <1 cm, well-defined margins, no extrathyroidal extension, metastasis, or high-risk cytologic/molecular features.
- For a tumor size of 1 to 4 cm (without extrathyroidal extension and N0 disease), lobectomy or total thyroidectomy is reasonable.
- Following treatment, patients are stratified into low-risk, intermediate-risk, or high-risk groups. Surveillance is guided by risk category, while thyroglobulin and imaging studies define treatment response.
- TSH initially is maintained between 0.5 and 3.0 mU/L in low-risk patients, 0.1 and 0.5 mU/L in intermediate-risk patients, and < 0.1 mU/L in high-risk patients.

ACTIVE SURVEILLANCE AS A MANAGEMENT STRATEGY FOR LOW-RISK PAPILLARY THYROID CARCINOMA

Rationale for Active Surveillance

In recent decades, epidemiologic studies have reported a significant increase in the incidence of thyroid cancer, yet mortality has remained relatively unchanged. These trends may be attributed to increased detection of papillary thyroid microcarcinoma (PTMC), which is defined by a tumor size of lesser than 1 cm and typically has an indolent course and an excellent prognosis.[1] Several studies have noted a disease-specific mortality rate of lesser than 1% and distant recurrence rates of 1% to 2% for PTMC.[2,3] The customary treatment of PTMC is a thyroid lobectomy or total thyroidectomy, each of which have associated morbidity, for example, recurrent laryngeal

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Endocrinol Metab Clin N Am 54 (2025) 329–340
https://doi.org/10.1016/j.ecl.2025.03.007 **endo.theclinics.com**

Abbreviations	
AS	active surveillance
CT	computed tomography
DFS	disease-free survival
DSS	disease-specific survival
DTC	differentiated thyroid carcinoma
FDG-PET	fluorodeoxyglucose-positron emission tomography
PFS	progression-free survival
PTC	papillary thyroid carcinoma
PTMC	papillary thyroid microcarcinoma
RCT	randomized controlled trial
Tg	thyroglobulin

nerve injury or hypocalcemia, and therefore avoiding possible unnecessary surgery in patients with indolent disease is of significant interest.

Prospective Studies Evaluating Active Surveillance

Two landmark prospective studies from Japan initially addressed the possibility of active surveillance (AS) of T1aN0M0 PTMC rather than employing thyroid surgery. In 1 study, 1235 patients with T1aN0M0 disease were followed for an average of 60 months. In 10-year follow-up, only 8% showed evidence of tumor enlargement (>3 mm) and 3.8% had evidence of nodal metastasis. Furthermore, 191 eventually underwent surgical resection following a period of observation, with only 1 patient developing tumor recurrence following resection.[4] A smaller study found that in 230 patients with T1aN0M0 disease followed for an average of 5 years, 90% of PTMCs were unchanged in size, and no patients developed extrathyroidal invasion or distant metastasis. No cases of disease recurrence were noted in the small minority of patients who were treated with surgical resection for disease progression.[5] Since these studies, some institutions have adopted AS of T1aN0M0 disease in selected patients as their standard practice.[6]

Others have since turned their attention to AS of T1bN0M0 disease, which is defined as a tumor greater than 1 cm but $\leq$2 cm in greatest dimension without extrathyroidal invasion. One study followed 61 patients for an average of 7.9 years, with 7% exhibiting tumor enlargement (>3 mm) and 3% with evidence of nodal metastasis. Six patients opted for surgery following disease progression, with no cases of recurrence following surgery.[1] Similar results were seen in other studies,[7–9] though all were limited by an average follow-up of no more than 32 months. Notably, all studies included primarily patients with tumor size lesser than 1.5 cm, that is, smaller T1b tumors.

Identifying Patients at Increased Risk for Progression During Active Surveillance

Age is highly predictive of disease progression during AS. For example, 10-year risk of progression in patients more than age 60 is 2.5%, compared to 22.5% in patients lesser than age 40.[4] Ultrasound characteristics have been evaluated as well. Studies from Japan and Korea have reported contradictory results regarding tumor calcification as a risk factor for progression.[10,11] On the other hand, rich tumor vascularity portends a higher risk of tumor progression compared to those with poor vascularity.[11] Molecular markers such as BRAF have not been able to consistently identify PTMC cases at low-risk of progression.[12,13] Molecular analyses were not in the inclusion and exclusion criteria of the prospective studies evaluating AS.

Who Are Ideal Candidates for Active Surveillance?

A risk stratification framework for selecting ideal candidates for AS has now been developed since the 2015 ATA guidelines. Ideal candidates are considered older patients (age >60) with a solitary thyroid nodule with well-defined margins and greater than 2 mm of normal surrounding parenchyma, no evidence of extrathyroidal extension, nodal metastasis, distant metastasis, or high-risk cytologic/molecular features.[14] Patients with a family history of papillary thyroid carcinoma (PTC), a genetic disorder associated with PTC, or a history of radiation to the neck are generally not considered as candidates for AS.

THYROID LOBECTOMY AS A TREATMENT OPTION FOR SELECTED DIFFERENTIATED THYROID CARCINOMAS

Oncologic Considerations for Thyroid Lobectomy

Historically, total thyroidectomy was recommended as initial surgical management for all differentiated thyroid carcinomas, which was justified primarily by retrospective data suggesting a slightly higher 10-year overall survival (OS) rate and a slightly lower 10-year overall recurrence rate.[15] However, significant limitations were noted in the quality of the data, for example, lack of data regarding extrathyroidal extension or completeness of resection.[6] Multiple retrospective studies derived from the National Cancer Database and the SEER database have since demonstrated no survival advantage with thyroidectomy in properly selected patients (see definition in section entitled *Optimal candidates for thyroid lobectomy*).[16–19] Interestingly, these results were seen despite the fact that a few of these studies included a significant minority of patients with high-risk features (tumor size >4–5 cm, extrathyroidal extension) who would not be considered candidates for lobectomy under current guidelines.[6] Similar survival outcomes were found in subsequent retrospective single-center studies.[20,21] Another single-center study noted that at 1 year follow-up after lobectomy, only 71.6% patients in a cohort of 164 patients had an excellent response, as defined by a serum thyroglobulin (Tg) level of lesser than 30 ng/mL.[22] However, there are significant limitations in the interpretation of Tg level following lobectomy,[23] and of the small number of patients requiring completion thyroidectomy, only 1.8% had histologically-confirmed disease recurrence. In a similar study, 95.6% of patients were in remission after an average follow-up of 19.1 years,[24] and patients with locoregional or metastatic recurrence were more likely to have aggressive histology or intermediate-risk features at baseline, which would have prompted initial total thyroidectomy under current guidelines.[6]

Optimal Candidates for Thyroid Lobectomy

The 2015 American Thyroid Association (ATA) guidelines and the 2024 National Comprehensive Cancer Network (NCCN) guidelines are largely in agreement. Both guidelines recommend total thyroidectomy for tumors T3 (ie, >4 cm in size) or greater, or with clinically apparent metastasis to lymph nodes (N1) or distant sites (M1); the NCCN guidelines further recommend total thyroidectomy in the case of aggressive histologic subtype, significant radiation exposure or family history of thyroid carcinoma, or coexistent thyroid disease. For patients with tumor size 1 to 4 cm, the 2015 ATA guidelines state that either lobectomy or total thyroidectomy is reasonable (assuming no extrathyroidal extension and N0 disease), but the latter is preferred if adjuvant RAI is anticipated or to facilitate interpretation of serum Tg measurements postoperatively. 2024 NCCN guidelines state that lobectomy is sufficient assuming negative resection margins, no evidence of contralateral disease, and N0 disease.

Both guidelines agree that for tumors lesser than 1 cm, if treatment is pursued at all, lobectomy alone is preferred assuming it is unifocal and confined to the thyroid, and in the absence of significant radiation exposure or family history of thyroid carcinoma.[6,25]

Benefits of Thyroid Lobectomy

While the complication rate of total thyroidectomy remains low when performed by a high-volume surgeon, the possibility of significant morbidity remains.[23] Overall, the pooled relative risk of complications is 10.67 for total thyroidectomy versus lobectomy,[26] with a relative risk of 1.85 for permanent paralysis of the recurrent laryngeal nerve, 1.69 for permanent hypoparathyroidism/hypocalcemia, and 2.58 for postoperative hematoma. Unsurprisingly, the risk of complications inversely varies with the annual volume of thyroid surgeries performed by the operating surgeon; the complication rate is 7.6% for surgeons performing more than 99 lobectomies annually compared to 11.8% for surgeons performing lesser than 10 lobectomies annually.[27] This is important because the majority of surgeons performing thyroid surgery are low-volume thyroid surgeons. For example, in 1 survey of 16,954 thyroidectomies, 51% of the surgeons performed less than 1 thyroidectomy annually.[28] In addition to a lower rate of surgical complications, patients receiving lobectomy might obviate the need for lifelong levothyroxine supplementation, which is invariably required after total thyroidectomy.[23]

Long-Term Considerations Following Thyroid Lobectomy

The possible need for adjuvant RAI should be considered when weighing the extent of the initial surgical resection for tumors 1 to 4 cm in size, as RAI is only considered effective once a total thyroidectomy has been performed.[23] According to the 2015 ATA guidelines, adjuvant RAI is preferred in patients with microscopic extrathyroidal extension or lymph node metastasis; thus, if these features are detected on histologic analysis following lobectomy, the patient might then require a completion thyroidectomy to facilitate adjuvant RAI administration.[6] For example, a retrospective cohort study noted that 19.5% of patients initially eligible for lobectomy would subsequently require completion thyroidectomy due to the indication for adjuvant RAI.[29]

The final consideration complicating the extent of surgical resection is the measurement of serum Tg postoperatively. Tg is a highly sensitive marker for disease recurrence, but its interpretation following lobectomy is controversial, as the remaining thyroid lobe produces significant Tg.[23] Traditionally, higher Tg cutoffs for detecting disease recurrence have been recommended following lobectomy. An excellent response has been defined as Tg lesser than 30 ng/mL, negative anti-Tg antibodies, and an unremarkable neck ultrasound; a biochemically incomplete response has been defined as Tg greater than 30 ng/mL or rising or increasing anti-Tg antibodies, and an unremarkable neck ultrasound.[30] However, several studies subsequently observed that Tg levels naturally rise as much as 10% annually, and that Tg levels were not significantly different in patients in remission or with recurrence.[31–33] Given the limitations of serum Tg in this setting, and the fact that most recurrences for low-risk carcinomas occur in the contralateral lobe or lymph nodes, some suggest using neck ultrasound with bilateral lymph node mapping as the primary means of surveillance following lobectomy.[23]

LONG-TERM SURVEILLANCE FOR RECURRENCE OF DIFFERENTIATED THYROID CARCINOMA

Rationale for Surveillance

In recent decades the number of survivors of differentiated thyroid carcinoma has climbed significantly, owing in large part to the increased incidence of incidentally-

detected low-risk disease coupled with static mortality rates from thyroid carcinoma. The majority of patients have a low risk of significant disease recurrence,[34] which is usually detected in the first 5 years after treatment, but can be detected decades after.[35] However, there are certain populations at high-risk for recurrence and mortality. For example, patients more than 70 years old have a 37-fold increased risk of death compared to patients lesser than 40 years old, and men are noted to have a 2.31-fold increased risk of recurrence relative to women (independent of TNM stage at presentation).[36,37] Most experts now advocate for a tailored, patient-specific approach to surveillance, with ongoing, dynamic evaluation of recurrence risk.[6,34]

Use of Serum Thyroglobulin and Antithyroglobulin Antibodies During Surveillance

In all patients with DTC, serum Tg is an integral part of the surveillance strategy. Whenever Tg is measured, an accompanying TSH and anti-Tg measurement should be obtained. Serum Tg production is stimulated by TSH, so a patient without adequate TSH suppression (ie, higher TSH levels than desired) could have a misleadingly high Tg compared to a Tg measurement obtained under TSH suppression. Measurement of anti-Tg antibodies is essential, as the commonly used immunometric assay only detects unbound Tg and not Tg complexed to anti-Tg antibodies. Thus, in a patient with anti-Tg antibodies, serum Tg can be falsely low (if measured by immunometric assay) and recurrence of disease may be missed. Some experts recommend use of a radioimmunoassay, which detects unbound Tg and complexed Tg, but this assay is not widely available.[38] Regardless of assay type, serial comparisons of Tg and anti-Tg antibody titers should be done using the same assay type. In a patient with anti-Tg antibodies, a rise in anti-Tg antibodies—with or without a concomitant rise in serum Tg—can indicate disease recurrence. For example, the risk of recurrence in patients with anti-Tg antibody greater than 100 units/mL is 18% to 49%, compared to a 1% to 3% risk of recurrence in patients with anti-Tg antibody lesser than 100 units/mL.[39,40]

Surveillance 2-Years Posttreatment

Following initial treatment, patients are classified as low (~5%), intermediate (~20%), or high-risk (50%) of recurrence according to 2015 ATA guidelines (**Table 1**).[6] During this period, all risk groups are recommended to have biannual non-TSH-stimulated Tg/anti-Tg antibody measurements and an annual neck ultrasound. Additional recommendations in intermediate-risk patients include a diagnostic whole-body RAI scan at 18 months posttreatment to screen for structural recurrence. High-risk patients additionally receive computed tomography (CT) of the neck and chest, as well as fluorodeoxyglucose-positron emission tomography (FDG-PET) at 12 months and 24 months post treatment.[6,34]

The recommended degree of TSH suppression, which minimizes the possibility of TSH stimulation causing tumor growth, varies according to the ATA risk category. TSH initially can be maintained between 0.5 and 3.0 mU/L in low-risk patients with undetectable Tg; between 0.1 and 0.5 mU/L in intermediate-risk patients; and lesser than 0.1 mU/L in high-risk patients.[6] TSH suppression goals are subsequently adjusted up or down pending the patient's clinical response.

Surveillance Beyond 2-Years Posttreatment

After the initial 2 year surveillance period, the response to initial therapy is classified into 1 of 4 categories: excellent, biochemically incomplete, structurally incomplete, or indeterminate (**Table 2**). This classification system was initially validated in patients post total thyroidectomy and RAI but has subsequently been validated in patients who

Table 1
Initial risk stratification of thyroid carcinoma recurrence following thyroidectomy

At a Low Risk (~5% Risk of Recurrence)	ATA Intermediate Risk (~20% Risk of Recurrence)	ATA High Risk (50% Risk of Recurrence)
PTC (with all of the following): • No local or distant metastases. • All macroscopic *tumor has* been resected. • No tumor invasion of loco-regional tissues or structures. • The tumor does not have aggressive histology (eg, tall cell, hobnail variant, columnar cell carcinoma). • If 131I is given, there are no RAI-avid metastatic foci outside the thyroid bed on the first posttreatment whole-body RAI scan. • No vascular invasion. • Clinical N0 or <5 pathologic N1 micrometastases (<0.2 cm in largest dimension). • Intrathyroidal, encapsulated follicular variant of PTC. • Intrathyroidal, well-differentiated follicular thyroid cancer with capsular invasion and no or minimal (<4 foci) vascular invasion. • Intrathyroidal, papillary microcarcinoma, unifocal or multifocal, including $BRAF^{V600E}$ mutated (if known).	• Microscopic invasion of tumor into the perithyroidal soft tissues. • RAI-avid metastatic foci in the neck on the first posttreatment whole-body RAI scan. • Aggressive histology (eg, tall cell hobnail variant, columnar cell carcinoma). • Papillary thyroid cancer with vascular invasion. • Clinical N1 or >5 pathologic N1 with all involved lymph nodes. • Multifocal papillary microcarcinoma with extrathyroidal extension and $BRAF^{V600E}$ mutated (if known).	• Macroscopic invasion of tumor into the perithyroidal soft tissues (gross extrathyroidal extension). Incomplete tumor resection. • Distant metastases. • Postoperative serum Tg suggestive of distant metastases. Pathologic N1 with any metastatic lymph node >3 cm in largest dimension. • Follicular thyroid cancer with extension vascular invasion (>4 foci of vascular invasion).

Data from 2015 American Thyroid Association Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer: The American Thyroid Association Guidelines Task Force on Thyroid Nodules and Differentiated Thyroid Cancer.[6]

received lobectomy or total thyroidectomy without RAI.[30,33] Response to therapy should be reassessed—with possible revision of the surveillance strategy—at each follow-up clinic visit.

Patients initially deemed at low-risk or intermediate-risk for recurrence and with an excellent response 2 years posttreatment do not require further surveillance.[41,42] In these patients, the cost effectiveness of more prolonged or more frequent surveillance is not justified[43]; however, some centers obtain annual nonstimulated Tg along with neck ultrasound at 5 year intervals.[6,34] For patients with any response to treatment other than an excellent response, typical management entails a nonstimulated Tg

Table 2
Classification of patient response to initial treatment of thyroid carcinoma

Excellent response	Negative imaging, and either: • Nonstimulated Tg <0.2 ng/mL Or • TSH-stimulated Tg <1 ng/mL
Biochemical incomplete response	Negative imaging, and either: • Nonstimulated Tg >1 ng/mL Or • TSH-stimulated Tg >10 ng/mL Or • Rising anti-Tg antibody
Structural incomplete response	Structural or functional evidence of disease, with: • Any Tg level • Presence or absence of anti-Tg antibodies
Indeterminate response	Any of: • Nonspecific findings on imaging studies • Faint uptake in thyroid bed on RAI scanning • Nonstimulated Tg detectable, but <1 ng/mL • TSH-stimulated Tg detectable, but <10 ng/mL Or • Anti-Tg antibodies stable or declining in the absence of structural or functional disease.

Data from 2015 American Thyroid Association Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer: The American Thyroid Association Guidelines Task Force on Thyroid Nodules and Differentiated Thyroid Cancer.[6]

biannually and annual ultrasound for 5 years, with possible biannual biochemical and structural evaluation in the indeterminate response group.[6,34]

Patients with a structural incomplete response require the most aggressive surveillance strategy. In additional to cervical ultrasound as outlined above, typically these patients receive a baseline diagnostic whole-body RAI scan to determine RAI avidity (to assess for possible disease dedifferentiation and for treatment implications), baseline FDG-PET (to assess for distant metastases, particularly those that are dedifferentiated and not RAI avid), and biannual to annual cross-sectional CT or MRI to assess for disease progression.[6,34] Further studies such as bone scan and brain MRI may be indicated in certain patients.

THYROID-STIMULATING HORMONE (TSH) SUPPRESSION AS PART OF LONG-TERM MANAGEMENT OF THYROID CANCER

Rationale for TSH Suppression

TSH suppression therapy as part of long-term management of intermediate-risk and high-risk differentiated thyroid cancer has been used to prevent potential stimulation of TSH receptors on DTC cells, and tumor growth.

TSH Suppression Goals

Current ATA guidelines recommend TSH suppression to below 0.1 mU/L in patients with high-risk thyroid cancer and chronically in patients with a structural incomplete response to therapy. These guidelines suggest a TSH goal of 0.1 to 0.5 mU/L in intermediate-risk and low-risk patients who have undergone remnant ablation and have low-level serum Tg levels, in addition to patients with an incomplete biochemical response to therapy. Those recommendations were based on low-moderate quality evidence.[6]

Evidence Supporting Benefits and Harms of TSH Suppression

The National Thyroid Cancer Treatment Cooperative Study Group Registry suggested that in high-risk patients, levothyroxine suppressive treatment with a target of undetectable serum TSH (ie, TSH <.01 mU/L) was associated with decreased rates of disease recurrence and cancer-related mortality. However, when factors such as radioiodine therapy and age were considered, TSH suppression was not shown to be statistically significant.[44]

Subsequent studies have noted that subnormal serum TSH levels were associated with improved OS and disease-specific survival (DSS) in patients with Stage 2 DTC. For patients with Stage 3 and 4 DTC, subnormal to undetectable serum TSH levels were linked to better survival outcomes.[45] Even in cases of distant metastatic disease, moderate TSH suppression was associated with significantly improved 1 to 3 year OS and disease-free survival (DFS), while more aggressive TSH suppression did not yield additional benefits.[46]

In a subsequent multicenter retrospective cohort study of intermediate-risk and high-risk DTC patients, TSH suppression did not result in better OS or progression-free survival (PFS). However, it was limited by a low mortality rate.[47]

In a randomized controlled trial (RCT) designed as a noninferiority study that compared TSH suppressive therapy with replacement levothyroxine therapy in 441 DTC patients, there was no significant difference in DFS, DSS, overall recurrence rates, or recurrence sites between patients receiving TSH suppression and those who did not.[48] The second RCT, which included a smaller patient group (76 patients), also found no significant differences in DFS and OS between the 2 groups, although a significant difference was noted for high-risk patients.[49]

A comprehensive meta-analysis by Gubbi and colleagues examined the association between TSH suppression and survival in intermediate-risk and high-risk DTC patients. The analysis included 9 trials and found no significant difference in PFS, DFS, or relapse-free survival between TSH suppression and nonsuppression groups. Additionally, a secondary analysis revealed a higher risk of cardiovascular and skeletal complications in TSH-suppressed patients.[50]

In 2021, a separate meta-analysis by Lee and colleagues reported that patients with exogenous subclinical hyperthyroidism experienced increased heart rate, left ventricular mass index, and interventricular septal thickness, highlighting the potential adverse effects of TSH suppression.[51]

In conclusion, there are still more questions than answers regarding the recommended level of TSH suppression, especially in patients with intermediate-risk DTC, and more randomized studies are needed to clarify the benefit of TSH suppression according to age, tumor histology, genotype, and extent of metastasis. The recommendation to target TSH suppression in patients with DTC should be weighed against potential side effects on an individualized basis.

CLINICS CARE POINTS

- Ideal candidates for active surveillance of low-risk differentiated thyroid cancer are: older patients (age >60) with a solitary thyroid nodule (usually <1 cm in size) and no intermediate or high-risk features.
- For patients with tumor size 1 to 4 cm, the 2015 ATA guidelines state that either lobectomy or total thyroidectomy is reasonable for initial surgical management.
- Following initial treatment, patients are classified as low-risk, intermediate-risk, or high risk of recurrence.

- All risk groups are recommended to have biannual non-TSH-stimulated Tg/anti-Tg antibody measurements and an annual neck ultrasound, with additional studies for intermediate-risk or high-risk patients.
- TSH initially can be maintained between 0.5 and 3.0 mU/L in low-risk patients with undetectable Tg; between 0.1 and 0.5 mU/L in intermediate risk patients; and <0.1 mU/L in high risk patients.

DISCLOSURES

W. Kuenstner and Y. Alzedaneen have no disclosures to report. K.D. Burman has written clinical review articles for UpToDate.

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