Treatment strategies for low-risk papillary thyroid carcinoma: a position statement from the Thyroid Department of the Brazilian Society of Endocrinology and Metabolism (SBEM)

Laura Sterian Ward
https://orcid.org/0000-0003-1601-3220

Rafael Selbach Scheffel
https://orcid.org/0000-0002-8858-309X

Ana O. Hoff
https://orcid.org/0000-0002-7058-6321

Carolina Ferraz
https://orcid.org/0000-0002-6620-4826

Fernanda Vaisman
https://orcid.org/0000-0002-6835-7108

ABSTRACT
Increasingly sensitive diagnostic methods, better understanding of molecular pathophysiology, and well-conducted prospective studies have changed the current approach to patients with thyroid cancer, requiring the implementation of individualized management. Most patients with papillary thyroid carcinoma (PTC) are currently considered to have a low risk of mortality and disease persistence/recurrence. Consequently, current treatment recommendations for these patients include less invasive or intensive therapies. We used the most recent evidence to prepare a position statement providing guidance for decisions regarding the management of patients with low-risk PTC (LRPTC). This document summarizes the criteria defining LRPTC (including considerations regarding changes in the TNM staging system), indications and contraindications for active surveillance, and recommendations for follow-up and surgery. Active surveillance may be an appropriate initial choice in selected patients, and the criteria to recommend this approach are detailed. A section is dedicated to the current evidence regarding lobectomy versus total thyroidectomy and the potential pitfalls of each approach, considering the challenges during long-term follow-up. Indications for radioiodine (RAI) therapy are also addressed, along with the benefits and risks associated with this treatment, patient preparation, and dosage. Finally, this statement presents the best follow-up strategies for LRPTC after lobectomy and total thyroidectomy with or without RAI. Arch Endocrinol Metab. 2022;66(4):522-32.

Keywords
Papillary thyroid carcinoma; position statement; active surveillance

INTRODUCTION
We have witnessed over the last decade a paradigm shift in terms of staging and management of patients with papillary thyroid carcinoma (PTC) from a standardized approach to individualized assessment and treatment. These changes have occurred mostly due to the development of risk assessment tools that have allowed early prediction during follow-up of meaningful outcomes such as disease-specific mortality and risks of structural disease persistence/recurrence or therapeutic failure. The approach to individualized PTC management is built on the importance of tumor histology, quality of the first surgery, serum thyroglobulin (Tg) levels in the postoperative evaluation, and decisions regarding the choices for the initial therapy and adjuvant therapy with radioactive iodine (RAI) (1). Based on this approach, most patients with PTC are classified as having a low risk of mortality and persistence/recurrence disease and, for this reason, the current recommendations include less invasive or intensive therapies (2,3).
Assessing the mortality risk

Death is usually the primary concern of patients with cancer during the first office appointment. Hence, an accurate classification to predict cancer-specific mortality is crucial. As with other solid tumors, the American Joint Committee on Cancer (AJCC) staging system, known as TNM (tumor, node, and metastasis), is widely used in PTC. This staging system considers the tumor size and local invasion by the primary tumor and the presence of metastatic lymph nodes and distant metastases, all divided by age group. The AJCC/TNM system performs well compared with other staging classifications and is the most used system in tumor registries worldwide. The recent AJCC 8th edition has brought a few changes that seem to enhance the accuracy of the prediction of diseasespecific mortality (4, 5). Three main changes are worth mentioning. First, the cutoff age at diagnosis increased from 45 to 55 years. This change was supported by an international multicenter study with almost 10,000 patients showing that the age of 55 years was better at separating patients with stages III versus IV disease (6). Second, the AJCC 8th edition reevaluated the prognostic significance of minor extrathyroidal extension (mETE), defined as subclinical perithyroidal invasion only detectable on histology (i.e., not apparent on intraoperative inspection or imaging evaluation). The prior AJCC 7th edition had classified any tumor with mETE as T3, but studies have shown that mETE alone has no influence on disease-free survival or disease-specific survival, despite conflicting data regarding its influence on persistence/recurrence of disease in thyroid bed or cervical lymph nodes. Additionally, a recent study by Tam and cols. has suggested that tumor size is an independent predictor of those outcomes (7). Considering these factors, the AJCC 8th edition has subdivided the T3 classification into T3a for tumors above 4 cm confined to the thyroid gland and T3b for tumors with ETE defined as gross strap muscle invasion. The third change in the AJCC 8th edition that is worth mentioning is regarding mediastinal metastatic lymph nodes, referred to as level VII lymph nodes. Previously, N1a was used only when metastatic lymph nodes were found in level VI (central compartment, i.e., pretracheal, paratracheal, or prelaryngeal). Now, metastases to these mediastinal lymph nodes are categorized as N1a, while N1b is used for metastatic lymph nodes in the lateral neck (8, 9). Additionally, older patients with N1 disease are no longer upstaged to stage III or IV disease (2); patients with N1 disease who are younger or older than 55 years are now classified as having stage I or II disease, respectively.

Multiple publications have demonstrated that, compared with the AJCC 7th edition, the 8th edition downstages a substantial number of low-risk patients and provides better separation between stage groups (7, 9, 10). Most (>90%) patients are categorized into stages I and II and have a risk of cancer-related death below 1% (11).

Assessing disease persistence/recurrence

Considering that patients with DTC have very low mortality rates, assessing these patients’ risk based on disease persistence/recurrence seems to be more adequate. Hence, stratification based on histopathological features, presence of lymph node and distant metastases, and some postoperative information such as response to therapy has been endorsed (5). Based on these considerations, the American Thyroid Association (ATA) risk-stratification system has been widely used. This system classifies patients into the following three categories of disease recurrence or persistence (2): low-risk (<5%), intermediate-risk (5%-20%), and high-risk (>20%). This risk assessment is currently based on histopathological features of the tumor and will likely include molecular features in the near future. Additionally, operative findings (not described in the pathological report) including vocal cord paralysis, extent of gross extrathyroidal invasion, and completeness of resection, should be considered in the risk assessment. Patients with low-risk disease encompass 57% of all patients with PTC (12). This category of low-risk disease includes (2):

- Patients with very low risk of recurrence (< 1%, unifocal, tumor size < 1 cm if PTC),
- Patients with PTC with intrathyroidal tumors < 4 cm, without clinical evidence of lymph node metastases or with ≤ 5 microscopic (< 2 mm) lymph node metastases on histology, without vascular invasion, and without an aggressive variant of PTC, and
- Patients with well-differentiated follicular thyroid cancer with capsular invasion alone or with less than four foci of vascular invasion.

Molecular characterization of the tumor has not been adopted routinely yet, and the impact of BRAF or other (e.g., TERT) mutations on risk assessment is still a matter of debate (13, 14).
Definition of low-risk papillary thyroid carcinoma

A better understanding of the prognostic tools in PTC has clarified the favorable course of patients with low-risk disease and opened the discussion about the best approach in such cases. The management options for these patients have expanded, ranging from simple observation (active surveillance [AS]) to total thyroidectomy (TT) with or without adjuvant RAI therapy. These decisions must be individualized and adapted according to the resources available at each center.

Given these considerations, we present herein the recommendations of the Brazilian Society of Endocrinology and Metabolism regarding the management of low-risk PTC (LRPTC) based on the ATA 2015 guidelines (2). Depending on age, tumor size with no extrathyroidal invasion, and lymph node status (less than 5 AND all less than 0.2 cm), patients classified as having AJCC/TNM stage I or II will be considered to be at low risk for structural disease recurrence and disease-specific death.

ACTIVE SURVEILLANCE

The strategy of AS was initially recommended for the management of microPTC. This strategy prevents excessive early treatment, among other advantages. Monitoring of microPTC gained recognition in 2010 when a pioneer group published the first data showing safe follow-up of patients with microPTC managed without intervention and in whom the tumor was clearly visualized on ultrasonography (US) (15).

Guidelines recommend AS as the initial approach in selected patients with microPTC (2,16-18). In addition to recommending AS for lesions < 1 cm, the ATA guidelines also recommend this approach to low-risk, completely intrathyroidal tumors measuring up to 1.5 or 2 cm (2). Several studies from different countries have confirmed initial data from Japan that has shown nodular growth in approximately 10% of the patients with microPTC and lymph node metastasis in less than 5% of them, with none of the studies describing distant metastases or death during AS (19-24). Fewer studies have included tumors measuring up to 1.5 or 2.0 cm tumors (2); Figure 1 includes microPTC as we need more data regarding larger tumors.

Indications and contraindications for active surveillance

Before a patient is started on AS, three main points must be evaluated, i.e., the characteristics of the nodule, characteristics of the patient, and characteristics of the team that will follow the patient. This initial analysis will identify if the patient is an ideal, appropriate, or inappropriate candidate for AS (25) (Table 1). Patients considered to be an ideal candidate for AS in this initial analysis and who fulfilled all criteria should be offered AS along with the information that future surgery may be necessary if the nodule grows in size or signs of (lymph nodes or distant) metastases emerge, or at the patient’s discretion. In contrast, patients who do not fit into any of the three categories should be referred for thyroidectomy.

Of note, these nodules have an approximate 50% chance of growth over 10 years in patients younger than 40 years, particularly in those closer to the age of 20 years (26,27). Still, the prognosis is not affected if AS is chosen for these patients and future surgery is required due to nodular growth (28).

Special situations

Family history

Familial nonmedullary thyroid carcinoma has a prevalence of around 3%-10% and is defined as the presence of nonmedullary thyroid carcinoma in at
Table 1. Patient classification as ideal, appropriate, and inappropriate to initiate AS

| Nodule characteristics | Ideal | Appropriate | Inappropriate |
|------------------------|-------|-------------|--------------|
| Solitary nodule        |       | Multifocal  |              |
| Well-defined margins   |       | Subcapsular |              |
| pN0, cM0               |       | Location (not adjacent to RLN) |              |
| No extrathyroidal       |       | Background US findings |              |
| extension               |       |             | Aggressive cytology |
|                        |       |             | Subcapsular location adjacent to RLN |
|                        |       |             | Obtuse angles between tumors and the trachea |
|                        |       |             | cN1, cM1 |
|                        |       |             | Evidence of extrathyroidal extension |

| Patient characteristics | Ideal | Appropriate | Inappropriate |
|-------------------------|-------|-------------|--------------|
| >60 years               |       | 18 to 59 years | <18 years |
| Acceptance (also family members) |       | Strong family history of PTC | Unlikely to make follow-up |
| Follow-up plans         |       | Childbearing potential | No acceptance |
| Life-threatening comorbidities |       | “Minimalistic” | “Maximalist” |

| Medical team characteristics | Ideal | Appropriate | Inappropriate |
|------------------------------|-------|-------------|--------------|
| Experienced multidisciplinary team |       | Experienced endocrinologist/surgeon | US not available |
| High quality US              |       | US routinely available | Little available with thyroid cancer management |
| Prospective data collection  |       |             |              |
| Reminder program to ensure follow-up |       |             |              |

RLN: recurrent laryngeal nerve; US: ultrasound; PTC: papillary thyroid carcinoma.
Modified from: Brito and cols. (25).

least three first-degree relatives in the absence of other known familial syndromes (29). Although some studies have shown that the risk of recurrence or mortality is comparable in cases of familial versus sporadic nonmedullary thyroid carcinoma, familial cases appear to have an increased risk of multifocal lesions (30-32). Although AS may be a therapeutic option in confirmed cases of familial microPTC, surgery is a better choice and TT should be recommended in these cases (28).

**Childbearing age or pregnancy**

Despite a few reports associating levels of beta human chorionic gonadotropin (hCG) with increased number and volume of thyroid nodules during pregnancy (33,34), the aggressiveness of these tumors is not increased (35). Therefore, women of childbearing age or pregnant who are diagnosed with microPTC may also undergo AS following the same criteria shown in Table 1, however, more studies with long follow-up are needed in pregnant women and those who want to become pregnant.

**Concomitant thyroid disorders (Graves’ disease, Hashimoto’s thyroiditis, associated benign nodules)**

Although evidence shows an increased risk of thyroid cancer in patients with autoimmune diseases (36), AS is currently not contraindicated in patients with Graves’ disease or Hashimoto’s thyroiditis (28,36). However, two aspects must be kept in mind regarding these patients. The first is that they should be maintained euthyroid to prevent stimulation of nodular growth due to high TSH values, and the second is to assess whether the heterogeneity of the thyroid on US could impair the measurement and proper follow-up of the tumor (2).

Regarding the presence of associated benign nodules, treatment is not required when these nodules are not clinically significant (e.g., toxic nodules or bulky nodules leading to compressive symptoms) (2,28).

**TSH suppression therapy during active surveillance**

Evidence of benefits from levothyroxine suppressive therapy in patients undergoing AS remains inconclusive since no randomized trials have been conducted to evaluate this effect. At the moment, the safest strategy to prevent nodular growth and deleterious effects from excessive thyroid hormone (especially in elderly patients) is to maintain TSH values within the normal range (2,28).

**Follow-up and indications for surgery**

Patients undergoing AS must be reassessed at each visit, with a focus on the characteristics of the nodule and the ability of the patient and the staff to continue AS (Figure 1). Neck CT may be helpful in cases of nodules close to or in contact with the trachea in order to better visualize the contact angle between them. An obtuse angles between tumors and the trachea should be indication for surgery (Table 1).

Indications for surgery during AS include a > 3 mm growth in tumor size, growth of the tumor to a diameter ≥ 13 mm, detection of lymph node metastasis, diagnosis of other thyroid or parathyroid disease, or a change in
the patient’s therapeutic preference. Based on current recommendations, clinical and US assessments and appointments should be performed every 6 months for the first 2 years and annually thereafter, if no clinical or ultrasonographic changes, have been suggested (25,28).

Special considerations before the implementation of active surveillance in Brazil

Before AS is implemented at a center, some points must be considered to ensure that the patients will be safely followed up:

1. The medical team that will follow the patient must be experienced in managing thyroid cancer. Additionally, within the team and between the team and the other doctors caring for the patient there must be a consensus regarding the patient’s management.

2. The medical team must be prepared at all stages of follow-up to clarify the patients’ concerns regarding treatment indications and contraindications, reassure the patients and help them overcome their fears, and be available to talk to the patients and their families.

3. The infrastructure of the center should facilitate the patient’s follow-up, ensuring the availability of appointments within the specified follow-up period. The center must also ensure the availability of quality US during follow-up or, when possible, offer quality US within its premises.

4. Centers without experience with AS should choose to follow the patient under a research protocol.

SURGICAL TREATMENT

Lobectomy versus total thyroidectomy

The choice between TT (with or without RAI therapy) versus lobectomy has little impact on recurrence rates or risk of death from thyroid cancer. Solid evidence has shown that simple observation of the contralateral lobe is safe in patients with low-risk disease after lobectomy (2,37,38).

Indications for lobectomy versus total thyroidectomy

Partial thyroidectomy (PT) or lobectomy are considered to be sufficient in treating T1 and T2 tumors confined to the thyroid according to the ATA consensus, considering that the extent of the thyroidectomy has no effect on survival in PTC (39) and that recurrence after lobectomy is salvageable without a negative impact on the overall survival (2). Therefore, in our opinion, either PT or lobectomy is a good option for patients in Brazil, especially considering the limited number of head and neck surgeons with high surgical volume in the country. Notably, a systematic review and meta-analysis including 13,801 patients with microPTC (8,812 submitted to TT and 4,989 to PT) from 11 different cohorts has concluded that partial TT had equivalent results in terms of mortality, which is relatively low in these cases (40).

The maintenance of thyroid tissue in PT avoids the need for thyroid hormone replacement that inevitably results from a TT. In addition to an increased somatic and psychiatric burden, hypothyroidism may lead to a substantial socioeconomic impact in the form of early retirement or loss of income (41). However, even after lobectomy the need for hormone replacement is not uncommon, and half of the patients undergoing hemithyroidectomy may develop hypothyroidism (42). Beyond that, Tg levels may be more conveniently followed up after TT (43,44).

Completion thyroidectomy may be required in cases of persistent or recurrent disease. After lobectomy, a histopathological report showing evidence of lymph node or distant metastasis, or an increased number of risk factors for recurrence (such as ETE, aggressive variants, reported positive margins either by pathologist or gross disease invasion reported by the surgeon, extensive angioinvasion, or lymphovascular or neural invasion) should prompt completion thyroidectomy and RAI treatment for a more favorable follow-up. The optimal time for completion thyroidectomy with fewer complications has been suggested to be 3 months (45,46).

In summary, TT allows for Tg levels to be more conveniently followed up (especially when RAI is used) and may decrease recurrence rates but increases morbidity. In contrast, lobectomy is a less extensive surgery that preserves some intrinsic thyroid function. Recent evidence suggests that lobectomy is a cost-effective strategy in middle-aged patients with LRPTC. In contrast, AS is cost-effective beginning at the age of 69 years (47). Hence, the decision regarding the extent of the surgical treatment in LRPTC must involve both the surgeon and the endocrinologist and consider the patients’ beliefs, socioeconomic and cultural characteristics, and access to adequate health services. Table 2 summarizes the current evidence that may guide choices (48).
Table 2. Summary of the main advantages and disadvantages of partial thyroidectomy in comparison to total thyroidectomy

| Advantages of lobectomy versus total thyroidectomy | Disadvantages of lobectomy versus total thyroidectomy |
|---------------------------------------------------|----------------------------------------------------|
| Lower surgical risks                               | Risk of completion surgery to improve prognosis and/or administer radioactive iodine |
| Thyroid hormone supplementation may not be necessary | Patients may still require thyroid hormone supplementation (thyroiditis or little remaining parenchyma) |
| Comparable survival                                | No evidence of quality of life improvement |
| Completion surgery, if necessary, does not increase surgical risk neither modify outcome | Not adequate for intermediate- and high-risk patients |
| Thyroglobulin may not be appropriate for follow-up |

Modified from: Hartl DM, Guerlain J, Breuskin I, Hadoux J, Baudin E, Al Ghuzlan A, Terroir-Cassou-Mounat M, Lamartina L, Leboulleux S. Thyroid Lobectomy for Low to Intermediate Risk Differentiated Thyroid Cancer. Cancers (Basel). 2020 Nov 6;12(11):3282.

RADIOACTIVE IODINE TREATMENT

Postoperative RAI must be considered only in patients treated with TT and with the following goals (2,3):
1. Ablation (destruction of remaining thyroid tissue, which can improve the sensitivity of serum Tg measured during follow-up),
2. Adjuvant treatment (destruction of microscopic occult disease to reduce risk of recurrence),
3. Treatment (destruction of persistent or metastatic disease to improve disease-free survival or overall survival), and
4. Improved staging with post-treatment Whole body scan (WBS).

Radioactive iodine for remnant ablation

Previously, the role of remnant ablation was to facilitate postoperative follow-up and initial staging with measurement of stimulated Tg level and post-treatment WBS (12). However, with the advent of highly sensitive Tg assays and US, patients with LRPTC can be safely followed up without ablation of the normal thyroid tissue. After surgery, both serum Tg and cervical US can predict long-term prognosis and help decide whether to proceed or not with ablation (48). Patients with low-risk DTC and without Tg antibodies (TgAb) who present with normal neck US and serum Tg levels < 0.2 ng/mL on TSH suppression or < 1 ng/mL after recombinant TSH stimulation require no ablation (49,50). Notably, the performance and clinical impact of WBS have been questioned, and recent data have shown that this procedure has little impact on staging, especially in patients with low-risk or intermediate-risk disease (51,52). Furthermore, Janovsky and cols. also showed that in low risk patients, overtime, Tg levels usually decline without radioiodine ablation, suggesting that Tg trend can also be used to avoid unnecessary treatment in these patients, especially with negative post-operative ultrasound (53).

Radioactive iodine for adjuvant treatment

The decision to proceed with adjuvant RAI therapy should be based on the risks and benefits of RAI in patients with low risk of recurrence and on the fact that delayed detection of the disease does not reduce survival. Currently, the decision and recommendation for RAI treatment in this group of patients are based mostly on retrospective studies indicating no substantial effect of adjuvant RAI therapy on overall or disease-free survival (12,55) and on prospective data from the NTCTCSG registry in which multivariate analyses demonstrated no significant effect of RAI treatment in low-risk patients (56,57). The results from two undergoing prospective trials (ESTIMABL2 [NCT01837745] and IoN [NCT01398085] trials) in which patients are randomized to RAI versus no RAI therapy will be able to confirm the impact on overall or disease-free survival of postoperative adjuvant RAI in low-risk patients.
In summary, based on current evidence, adjuvant RAI treatment is not routinely recommended for risk reduction or with adjuvant intent in patients with a low risk of recurrence (2).

Preparation and recommended radiiodine activity
Considering that the recurrence rates are low and a delayed diagnosis of persistent or recurrent disease has no effect on survival, it is important to provide the lowest RAI activity to avoid unnecessary risks from radiation exposure. Several studies indicate that treatments with a RAI dose of 1.1 GBq (30 mCi) provide the same results as those with a dose of 3.7 GBq (100 mCi) (47,58-62). Additionally, studies comparing the preparation for RAI therapy using thyroid hormone withdrawal versus recombinant TSH administration have shown both strategies to be effective, although the use of recombinant TSH has been associated with better quality of life (49,60,61). Therefore, when RAI therapy is recommended, the preparation can be performed with recombinant TSH (when available), and the RAI dose can be low (1.1 GBq) and should be administered after 2 weeks of a low-iodine diet.

FOLLOW-UP STRATEGIES
The main goal of long-term follow-up in PTC is to detect disease recurrence in patients classified as being disease-free and progression in those with persistent disease. A second objective is to adequately manage the consequences of the initial treatment, including hypothyroidism and hypoparathyroidism. The risk of disease recurrence/persistence is low in LRPTC, as stated above, and the follow-up of patients with LRPTC differ according to the surgical treatment and the use or not of RAI (63). Patients on AS have a specific follow-up protocol, as described above.

The initial risk of recurrent/persistent disease should be refined during follow-up in light of the patient’s response to therapy 6-18 months after the initial treatment. It should be predominantly based on Tg level, detection of TgAb, and imaging findings (dynamic risk stratification). If the imaging study reveals persistent tumor foci, the patient’s response to treatment is classified as structurally incomplete. Conversely, if the imaging examination is negative, the response to treatment is classified as excellent if Tg and TgAb levels are undetectable, indeterminate if serum Tg levels are low, or biochemically incomplete if Tg levels are high (Table 3) (64).

Follow-up after lobectomy
The follow-up of patients treated with lobectomy is mainly based on the results of neck US. The emergence of benign nodules during follow-up (which occurs in 20%-50% of the patients) is far more common than tumor recurrence, which occurs in about 5% of all patients after lobectomy (37,65,66).

Table 3. Risk Stratification based on response to therapy 6-24 months after initial treatment (total thyroidectomy + RAI)

| Response to Therapy           | Definitions                                                                 |
|-------------------------------|-----------------------------------------------------------------------------|
| Excellent Response            | Nonstimulated Tg <0.2 ng/mL and/or Stimulated Tg <1 ng/mL + Undetectable TgAb + Negative imaging |
| Indeterminate Response        | Nonstimulated 0.2-1 ng/mL and/or Stimulated Tg 1-10 ng/mL and/or TgAb levels stable or declining and/or Nonspecific findings on imaging studies |
| Biochemical Incomplete Response | Abnormally elevated serum Tg and/or increasing Tg values over time with similar TSH levels and/or rising TgAb levels in the absence of localizable structural disease |
| Structural Incomplete Response | Persistent or newly identified loco-regional or distant metastases with or without abnormal Tg or TgAb |

Adapted from: Haugen and cols. (2) Tuttle and cols. (11) Momesso DP and cols. (67).

Tg: thyroglobulin; TgAb: thyroglobulin antibodies.
The proposed cutoff values for Tg in the assessment of treatment response are reported in Table 3. The temporal trend of Tg levels is more important than isolated Tg levels and can be a valuable guide during follow-up (44). A recent study of 1451 patients with PTC who underwent lobectomy has shown that postoperative Tg levels are reasonably valuable for surveillance. A Tg value of 5.3 ng/dL measured 6 to 12 months after lobectomy and a Tg cutoff value of 11.0 ng/mL with normal TSH for the most recent measurement have been shown to be good predictors of the risk of recurrence (68).

**Follow-up after total thyroidectomy with or without radiiodine**

The evaluation of the response to the initial treatment and the follow-up after TT are mainly based on Tg and TgAb levels. The values that define the response to treatment differ according to RAI treatment (Table 3).

The recurrence rates of patients with LRPTC classified as having an excellent response after the initial treatment is less than 2% (46). The follow-up of these patients can be limited to periodic (12 months) measurements of Tg and TgAb levels during levothyroxine therapy. The levothyroxine dose should be titrated to TSH levels in the normal or low range (0.5-2 IU/mL). After 5-10 years without evidence of disease, the risk of recurrence is so low that the need for routine assessments in specialized centers is debatable (69,70). Serum Tg measurements may be unable to identify small disease foci, particularly in the neck, which can be readily detected with neck US (71). However, the need for neck US monitoring is still a matter of debate since some studies have shown that the rate of false positive findings on neck US is high and may lead to inadequate treatment and/or follow-up (72,73). Furthermore, the effect of these early findings on patient outcomes has not been demonstrated, and the ATA guidelines recommend simple surveillance for suspicious lymph nodes with a < 10 mm (for lateral nodes) or < 8 mm (for central nodes) measurement in the short axis. We believe that in the absence of any other abnormalities in the first neck US, a subsequent US should not be scheduled before 3-5 years after the primary treatment, if ever (69,70).

An indeterminate response may be observed in 12%-23% of the patients with LRPTC, but 80%-90% of them will never experience disease recurrence (73,74). An analysis of stimulated Tg can be helpful in these cases. In patients with minimally increased stimulated Tg levels (< 2 ng/mL), Tg levels are likely to normalize spontaneously over time (73,74). Levels of Tg above 2 ng/mL are meaningful since the likelihood of persistent or recurrent disease increases with the increase in stimulated Tg levels. Up to 98% of the responses initially classified as indeterminate can be reclassified as excellent when stimulated Tg measurement is repeated 5 years after the initial treatment, compared with only 40% of the patients with an initial biochemical incomplete response (75). Also in these cases, the trend of Tg and TgAb values should be taken into consideration (44,75).

Only 10% of the patients with LRPTC treated with TT and RAI will show biochemical incomplete response (11). In this group of patients, serum Tg and TgAb levels should be monitored every 6-12 months, and neck US should also be performed yearly. Serial Tg measurements can be informative in these cases since Tg levels that are stable or decline over time indicate disease remission. Up to two thirds of these patients will later meet the criteria for an excellent response without any additional treatment (75-77). By contrast, serum Tg levels that rise over time are highly suspicious for persistent and/or recurrent disease (44,76) and should be explored with imaging studies.

In conclusion, the low mortality and recurrence/persistence rates of LRPTC allow for safe recommendations of different management approaches (Table 4). A multidisciplinary team can offer the best strategy considering the preferences of the patient, the experience of the medical team, and the characteristics associated with the patient’s quality of life.

Acknowledgment: this work was supported by the Thyroid Department of the Brazilian Society of Endocrinology and Metabolism.

Funding sources: the authors received no grants or fellowship support for the preparation of this document.

Author contributions: all authors have contributed equally to the study conception and design, data analysis and interpretation, and manuscript preparation. All authors have read and approved the final version of this manuscript.

Disclosure: no potential conflict of interest relevant to this article was reported.
Early decrease in the intensity and frequency of follow up and degree of TSH suppression

Low and intermediate risk:
Non stimulated Tg and TgAb every 12-24 months;
Consider neck US in 12-24 months, if negative, no need for further imaging

Indeterminate Response
Decrease in the intensity and frequency of follow up and degree of TSH suppression
Active surveillance:
Serial imaging of non specific lesions;
Non stimulated Tg and TgAb every 12-24 months

Biochemical Incomplete Response
Follow Tg curve with similar TSH levels.
Stable or declining Tg levels = Active surveillance
Non stimulated Tg and TgAb every 6-12 months,
Stimulated Tg if clinically indicated;
Neck US in 12 months.
TSH suppression (mild)
Increasing Tg or TgAb levels = Additional investigation
Individualized approach with anatomic, functional and/or hybrid imaging.
TSH suppression.

Structural Incomplete Response
Individualized approach:
Consider actionable and non-actionable structural evidence of disease.
TSH suppression

| Table 4. | Follow up strategies based on response to initial therapy |
|----------|--------------------------------------------------------|
| Excellent Response | Early decrease in the intensity and frequency of follow up and degree of TSH suppression |
| Indeterminate Response | Decrease in the intensity and frequency of follow up and degree of TSH suppression |
| Biochemical Incomplete Response | Follow Tg curve with similar TSH levels. Stable or declining Tg levels = Active surveillance |
| Structural Incomplete Response | Individualized approach: Consider actionable and non-actionable structural evidence of disease. |

REFERENCES

1. Rondeau G, Tuttle RM. Similarities and differences in follicular cell-derived thyroid cancer management guidelines used in Europe and the United States. Semin Nucl Med. 2011;41(2):89-95.

2. Haugen BR, Alexander EK, Bible KC, Doherty GM, Mandel SJ, Nikiforov YE, et al. 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. Thyroid. 2016;26(1):1-133.

3. Tuttle RM, Ahuja S, Avram AM, Bernet VJ, Bourguet P, Daniels GH, et al. Controversies, Consensus, and Collaboration in the Use of (131)I Therapy in Differentiated Thyroid Cancer: A Joint Statement from the American Thyroid Association, the European Association of Nuclear Medicine, the Society of Nuclear Medicine and Molecular Imaging, and the European Thyroid Association. Thyroid. 2019;29(4):461-70.

4. Brierey JD, Panzarella T, Tsang RW, Gospodarowicz MK, O’Sullivan B. A comparison of different staging systems predictability of patient outcome. Thyroid carcinoma as an example. Cancer. 1997;79(12):2414-23.

5. Tuttle RM, Haugen B, Perrier ND. Updated American Joint Committee on Cancer/Tumor-Node-Metastasis Staging System for Differentiated and Anaplastic Thyroid Cancer. (Eighth Edition): What Changed and Why? Thyroid. 2017;27(6):751-6.

6. Nixon J, Wang LY, Migliacci JC, Eskander A, Campbell MJ, Aniss A, et al. An International Multi-Institutional Validation of Age 55 Years as a Cutoff for Risk Stratification in the AJCC/UICC Staging System for Well-Differentiated Thyroid Cancer. Thyroid. 2016;26(3):373-80.

7. Tam S, Boonsripitayanon M, Amit M, Fellman BM, Li Y, Busaidy NL, et al. Survival in Differentiated Thyroid Cancer: Comparing the AJCC Cancer Staging Seventh and Eighth Editions. Thyroid. 2018;28(10):1301-10.

8. Randolph GW, Duh QY, Heller KS, LiVolsi VA, Mandel SJ, Steward DL, et al. The prognostic significance of nodal metastases from papillary thyroid carcinoma can be stratified based on the size and number of metastatic lymph nodes, as well as the presence of extranodal extension. Thyroid. 2012;22(11):1144-52.

9. van Velsen EFS, Stegenga MT, van Kemenade FJ, Kam BLR, van Ginthoven TM, Visser WE, et al. Comparing the Prognostic Value of the Eighth Edition of the American Joint Committee on Cancer/ Tumor Node Metastasis Staging System Between Papillary and Follicular Thyroid Cancer. Thyroid. 2018;28(8):876-81.

10. Nava CE, Zanella AB, Scheffel RS, Maia AL, Dora JM. Impact of the updated TNM staging criteria on prediction of persistent disease in a differentiated thyroid carcinoma cohort. Arch Endocrinol Metab. 2019;63(1):5-11.

11. Tuttle RM, Tata H, Shah J, Leboeuf R, Ghessein R, Gonon M, et al. Estimating risk of recurrence in differentiated thyroid cancer after total thyroidectomy and radioactive iodine remnant ablation: using response to therapy variables to modify the initial risk estimates predicted by the new American Thyroid Association staging system. Thyroid. 2010;20(12):1341-9.

12. Lamartina L, Durante C, Filetti S, Cooper DS. Low-risk differentiated thyroid cancer and radiiodine remnant ablation: a systematic review of the literature. J Clin Endocrinol Metab. 2015;100(5):1748-61.

13. Scheffel RS, de Cristo AP, Romitti M, Vargas CVF, Ceolin L, Zanella AB, et al. The BRAF(V600E) mutation analysis and risk stratification in papillary thyroid carcinoma. Arch Endocrinol Metab. 2021;64(6):751-7.

14. Scheffel RS, Dora JM, Maia AL. BRAF mutations in thyroid cancer. Curr Opin Oncol. 2021.

15. Sugitani I, Toda K, Yamada K, Yamamoto N, Ikenaga M, Fujimoto Y. Three distinctly different kinds of papillary thyroid microcarcinoma should be recognized: our treatment strategies and outcomes. World J Surg. 2010;34(6):1222-31.
16. Rosario PW, Ward LS, Graf H, Vaisman F, Mourao GF, Vaisman M. Thyroid nodules ≤ 1 cm and papillary thyroid microcarcinomas: Brazilian experts opinion. Arch Endocrinol Metab. 2019;63(5):456-61.

17. Russ G, Bonnema SJ, Erdogan MF, Durante C, Ngu R, Leonhardt L. European Thyroid Association Guidelines for Ultrasonography of Malignant Risk Stratification of Thyroid Nodules in Adults: The EU-TIRADS. Eur Thyroid J. 2017;6(5):225-37.

18. Takami H, Ito Y, Okamoto T, Yoshida A. Therapeutic strategy for differentiated thyroid carcinoma in Japan based on a newly established guideline managed by Japanese Society of Thyroid Surgery and Japanese Association of Endocrine Surgeons. World J Surg. 2011;35(1):111-21.

19. Kwon H, Oh HS, Kim M, Park S, Jeon MJ, Kim WG, et al. Active Surveillance for Patients With Papillary Thyroid Microcarcinoma: A Single Center’s Experience in Korea. J Clin Endocrinol Metab. 2017;102(6):1917-25.

20. Molinero E, Campopiano MC, Pieruzzi L, Matrone A, Agate L, Bottici V, et al. Active Surveillance in Papillary Thyroid Microcarcinomas is Feasible and Safe: Experience at a Single Italian Center. J Clin Endocrinol Metab. 2020;105(3).

21. Rosario PW, Mourao GF, Calсолari MR. Active Surveillance in Adults with Low-Risk Papillary Thyroid Microcarcinomas: A Prospective Study. Horm Metab Res. 2019;51(11):703-8.

22. Sanabria A. Experience with Active Surveillance of Thyroid Low-Risk Carcinoma in a Developing Country. Thyroid. 2020;30(7):985-91.

23. Smulever A, Pitoia F. Active surveillance in papillary thyroid carcinoma: not easily accepted but possible in Latin America. Arch Endocrinol Metab. 2019;63(5):462-9.

24. Tuttle RM, Fagin JA, Minkowitz G, Wong RJ, Roman B, Patel S, et al. Natural History and Tumor Volume Kinetics of Papillary Thyroid Cancers During Active Surveillance. JAMA Otolaryngol Head Neck Surg. 2017;143(10):1015-20.

25. Brito JP, Ito Y, Miyauchi A, Tuttle RM. A Clinical Framework to Facilitate Risk Stratification When Considering an Active Surveillance Alternative to Immediate Biopsy and Surgery in Papillary Microcarcinoma. Thyroid. 2016;26(1):144-9.

26. Ito Y, Miyauchi A, Kihara M, Higashiyama T, Kobayashi K, Miya A. Patient age is significantly related to the progression of papillary microcarcinoma of the thyroid under observation. Thyroid. 2014;24(1):27-34.

27. Miyauchi A, Kudo T, Ito Y, Oda H, Sasai H, Higashiyama T, et al. Estimation of the lifetime probability of disease progression of papillary microcarcinoma of the thyroid during active surveillance. Surgery. 2018;163(1):48-52.

28. Sugitani I, Ito Y, Takeuchi D, Nakayama H, Masaki C, Shindo H, et al. Indications and Strategy for Active Surveillance of Adult Low-Risk Papillary Thyroid Microcarcinoma: Consensus Statements from the Japan Association of Endocrine Surgery Task Force on Management for Papillary Thyroid Microcarcinoma. Thyroid. 2021;31(2):183-92.

29. Mazzhay H, Sippel RS. Familial nonmedullary thyroid carcinoma. Thyroid. 2013;23(9):1049-56.

30. Ito Y, Kakudo K, Hirao K, Kuboyama M, Yabuta T, Endo T, et al. Biological behavior and prognosis of familial papillary thyroid carcinoma. Surgery. 2002;131(5):837-9.

31. Lupoli G, Vitale G, Caraglia M, Fittipaldi MR, Abbruzzese A, Tagliaferri P, et al. Familial papillary thyroid microcarcinoma: a new clinical entity. Lancet. 1999;353(9153):637-9.

32. Uchino S, Noguchi S, Kawamoto H, Yamashita H, Watanabe S, Yamashita H, et al. Familial nonmedullary thyroid carcinoma characterized by multifocality and a high recurrence rate in a large population study. World J Surg. 2002;26(8):897-902.

33. Ballabio M, Poshychinda M, Ekins RP. Pregnancy-induced changes in thyroid function: role of human chorionic gonadotropin as putative regulator of maternal thyroid. J Clin Endocrinol Metab. 1991;73(4):824-31.

34. Shindo H, Amino N, Ito Y, Kihara M, Kobayashi K, Miya A, et al. Papillary thyroid microcarcinoma might progress during pregnancy. Thyroid. 2014;24(5):840-4.

35. Ito Y, Miyauchi A, Kudo T, Ota H, Yoshioka K, Oda H, et al. Effects of Pregnancy on Papillary Microcarcinomas of the Thyroid Reevaluated in the Entire Patient Series at Kuma Hospital. Thyroid. 2016;26(1):156-60.

36. Dias Lopes NM, Mendonca Lens HH, Armani A, Marinello PC, Cecchini AL. Thyroid cancer and thyroid autoimmune disease: A review of molecular aspects and clinical outcomes. Pathol Res Pract. 2020;216(9):153098.

37. Vaisman F, Shaha A, Fish S, Michael Tuttle R. Initial therapy with either thyroid lobectomy or total thyroidectomy without radioactive iodine remnant ablation is associated with very low rates of structural disease recurrence in properly selected patients with differentiated thyroid cancer. Clin Endocrinol (Oxf). 2011;75(1):112-9.

38. Welch HG, Doherty GM. Saving Thyroids – Overtreatment of Small Papillary Cancers. N Engl J Med. 2018;379(4):310-2.

39. Adam MA, Pura J, Gu L, Dinan MA, Tyler DS, Reed SD, et al. Extent of surgery for papillary thyroid cancer is not associated with survival: an analysis of 61,775 patients. Ann Surg. 2014;260(4):601-5; discussion 5-7.

40. Zheng W, Li J, Lv P, Chen Z, Fan P. Treatment efficacy between total thyroidectomy and lobectomy for patients with papillary thyroid microcarcinoma: A systemic review and meta-analysis. Eur J Surg Oncol. 2018;44(11):1679-84.

41. Thilum F, Brandt F, Brix TH, Hegedus L. Hypothyroidism is a predictor of disability pension and loss of labor market income: a Danish register-based study. J Clin Endocrinol Metab. 2014;99(9):3129-35.

42. Lee SJ, Song CM, Ji YB, Choi YY, Sohn YS, Park JH, et al. Risk factors for hypothyroidism and thyroid hormone replacement after hemithyroidectomy in papillary thyroid carcinoma. Langenbecks Arch Surg. 2021;406(4):1223-31.

43. Hartj DM, Guerlain J, Breuskin I, Hadoux J, Baudin E, Al Ghuzlan A, et al. Thyroid Lobectomy for Low to Intermediate Risk Differentiated Thyroid Cancer. Cancers (Basel). 2020;12(11).

44. Momesso DP, Vaisman F, Yang SP, Bulzico DA, Corbo R, Vaisman M, et al. Dynamic Risk Stratification in Patients with Differentiated Thyroid Cancer Treated Without Radioactive Iodine. J Clin Endocrinol Metab. 2016;101(7):2692-700.

45. Liu W, Yan X, Cheng R. Continuing controversy regarding individualized surgical decision-making for patients with 1-4 cm low-risk differentiated thyroid carcinoma: A systematic review. Eur J Surg Oncol. 2020;46(12):2174-84.

46. Dueñas JP, Duque CS, Cristancho L, Méndez M. Completion thyroidectomy in low-risk differentiated thyroid carcinoma: A systematic review and meta-analysis. Eur J Surg Oncol. 2020;46(12):2174-84.

47. Dueñas JP, Duque CS, Cristancho L, Méndez M. Completion thyroidectomy: is timing important for transcervical and remote access approaches? World J Otorhinolaryngol Head Neck Surg. 2020;6(3):165-70.

48. Youssef MR, Attia AS, Omar M, Aboueisha M, Freeman MN, Shama M, et al. Thyroid lobectomy as a cost-effective approach in low-risk papillary thyroid cancer versus active surveillance. Surgery. 2021.

49. Scheffel RS, Zanella AB, Antunes D, Dora JM, Maia AL. Low-risk papillary thyroid carcinoma: position statement. Arch Endocrinol Metab. 2022;66(4).
50. Matrone A, Gambale C, Piaggi P, Viola D, Giani C, Agate L, et al. Postoperative Thyroglobulin and Neck Ultrasound in the Risk Restratiﬁcation and Decision to Perform 131I Ablation. J Clin Endocrinol Metab. 2017;102(3):893-902.

51. Nava CE, Scheffel RS, Zanella AB, Zelmanovitz F, Maia AL, Dora JM. Reappraising the Diagnostic Accuracy of Post-Treatment Whole-Body Scans for Diﬀerentiated Thyroid Carcinoma. Horm Metab Res. 2020;52(12):834-40.

52. Agate L, Bianchi F, Brozzi F, Santini P, Molinaro E, Bottici V, et al. Less than 2% of the Low- and Intermediate-Risk Diﬀerentiated Thyroid Cancers Show Distant Metastases at Post-Ablation Whole-Body Scan. Eur Thyroid J. 2019;8(2):90-5.

53. Janovsky CC, Maciel RM, Camacho CP, Padovani RP, Nakabashi CC, Yang JH, et al. A Prospective Study Showing an Excellent Response of Patients with Low-Risk Diﬀerentiated Thyroid Cancer Who Did Not Undergo Radioiodine Remnant Ablation after Total Thyroidectomy. Eur Thyroid J. 2016;5(1):44-9

54. Lebouleux S, Bournaud C, Chougnet CN, Zerdoud S, Al Ghuzlan A, Catargi B, et al. Thyroidectomy without Radioiodine in Patients with Low-Risk Thyroid Cancer. N Engl J Med. 2022;388(10):923-32.

55. Schvartz C, Bonnettain F, Dabakuyo S, Gauthier M, Cuffe A, Fiefe S, et al. Impact on overall survival of radioactive iodine in low-risk differentiated thyroid cancer patients. J Clin Endocrinol Metab. 2012;97(5):1526-35.

56. Jonklaas J, Cooper DS, Ain KB, Bigos T, Brierley JD, Haugen BR, et al. Outcomes of patients with differentiated thyroid carcinoma following initial therapy. Thyroid. 2006;16(12):1229-42.

57. Janovsky CC, Maciel RM, Camacho CP, Padovani RP, Nakabashi CC, Yang JH, et al. A Prospective Study Showing an Excellent Response of Patients with Low-Risk Diﬀerentiated Thyroid Cancer Who Did Not Undergo Radioiodine Remnant Ablation after Total Thyroidectomy. Eur Thyroid J. 2016;5(1):44-9

58. Matrone A, Gambale C, Piaggi P, Viola D, Giani C, Agate L, et al. Postoperative Thyroglobulin and Neck Ultrasound in the Risk Restratiﬁcation and Decision to Perform 131I Ablation. J Clin Endocrinol Metab. 2017;102(3):893-902.

59. Nava CE, Scheffel RS, Zanella AB, Zelmanovitz F, Maia AL, Dora JM. Reappraising the Diagnostic Accuracy of Post-Treatment Whole-Body Scans for Diﬀerentiated Thyroid Carcinoma. Horm Metab Res. 2020;52(12):834-40.

60. Agate L, Bianchi F, Brozzi F, Santini P, Molinaro E, Bottici V, et al. Less than 2% of the Low- and Intermediate-Risk Diﬀerentiated Thyroid Cancers Show Distant Metastases at Post-Ablation Whole-Body Scan. Eur Thyroid J. 2019;8(2):90-5.

61. Jonklaas J, Cooper DS, Ain KB, Bigos T, Brierley JD, Haugen BR, et al. Outcomes of patients with differentiated thyroid carcinoma following initial therapy. Thyroid. 2006;16(12):1229-42.

62. Suss SKA, Mesa CO Jr, Camacho CP, Padovani RP, Nakabashi CC, Yang JH, et al. A Prospective Study Showing an Excellent Response of Patients with Low-Risk Diﬀerentiated Thyroid Cancer Who Did Not Undergo Radioiodine Remnant Ablation after Total Thyroidectomy. Eur Thyroid J. 2016;5(1):44-9

63. Lebouleux S, Bournaud C, Chougnet CN, Zerdoud S, Al Ghuzlan A, Catargi B, et al. Thyroidectomy without Radioiodine in Patients with Low-Risk Thyroid Cancer. N Engl J Med. 2022;388(10):923-32.

64. Jonklaas J, Cooper DS, Ain KB, Bigos T, Brierley JD, Haugen BR, et al. Outcomes of patients with differentiated thyroid carcinoma following initial therapy. Thyroid. 2006;16(12):1229-42.

65. Vaisman F, Momesso D, Builzico DA, Pessoa CH, da Cruz MD, Dias F, et al. Thyroid Lobectomy Is Associated with Excellent Clinical Outcomes in Properly Selected Diﬀerentiated Thyroid Cancer Patients with Primary Tumors Greater Than 1 cm. J Thyroid Res. 2013;2013:398194.

66. Matsuoka S, Sugino K, Masudo K, Nagahama M, Kitagawa W, Shibuya H, et al. Thyroid lobectomy for papillary thyroid cancer: long-term follow-up study of 1,088 cases. World J Surg. 2014;38(1):88-79.

67. Momesso DP, Tuttle RM. Update on differentiated thyroid cancer staging. Endocrinol Metab Clin North Am. 2014;43(2):401-21.

68. Xu S, Huang H, Zhang X, Huang Y, Guan B, Qian J, et al. Predictive Value of Serum Thyroglobulin for Structural Recurrence Following Lobectomy for Papillary Thyroid Carcinoma. Thyroid. 2021;31(9):1391-9.

69. Lamartina L, Handkiewicz-Junak D. Follow-up of low risk thyroid cancer patients: can we stop follow-up after 5 years of complete remission? Eur J Endocrinol. 2020;182(5):D1-16.

70. Imran SA, Chu K, Rajaraman M, Rajaraman D, Ghosh S, De Brabandere S, et al. Primary versus Tertiary Care Follow-Up of Low-Risk Diﬀerentiated Thyroid Cancer: Real-World Comparison of Outcomes and Costs for Patients and Health Care Systems. Eur Thyroid J. 2019;8(4):208-14.

71. Torlontano M, Attard M, Crocetti U, Tumino S, Bruno R, Costante G, et al. Follow-up of low risk patients with papillary thyroid cancer: role of neck ultrasonography in detecting lymph node metastases. J Clin Endocrinol Metab. 2004;89(7):3402-7.

72. Yang SP, Bach AM, Tuttle RM, Fish SA. Serial Neck Ultrasound Is More Likely to Identify False-Positive Abnormalities Than Clinically Significant Disease in Low-Risk Papillary Thyroid Cancer Patients. Endocr Pract. 2015;21(12):1372-9.

73. Vaisman F, Momesso D, Builzico DA, Pessoa CH, Dias F, Corbo R, et al. Spontaneous remission in thyroid cancer patients after biochemical incomplete response to initial therapy. Clin Endocrinol (Oxf). 2012;77(1):132-8.

74. Landenberger GMC, de Souza Salerno ML, Golbert L, de Souza R, et al. Primary versus Tertiary Care Follow-Up of Low-Risk Differentiated Thyroid Cancer: Real-World Comparison of Outcomes and Costs for Patients and Health Care Systems. Eur Thyroid J. 2019;8(4):208-14.

75. Lamartina L, Montesano T, Trulli F, Attard M, Torlontano M, Bruno R, et al. Papillary thyroid carcinomas with biochemical incomplete or indeterminate responses to initial treatment: repeat stimulated thyroglobulin assay to identify disease-free patients. Endocrine. 2016;54(2):467-75.

76. Durante C, Montesano T, Attard M, Torlontano M, Monzani F, Costante G, et al. Long-term surveillance of papillary thyroid cancer patients who do not undergo postoperative radioiodine remnant ablation: is there a role for serum thyroglobulin measurement? J Clin Endocrinol Metab. 2012;97(9):2748-53.

77. Vaisman F, Tala H, Grewal R, Tuttle RM. In differentiated thyroid cancer, an incomplete structural response to therapy is associated with significantly worse clinical outcomes than only an incomplete thyroglobulin response. Thyroid. 2011;21(12):1317-22.