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# Risk-oriented concept of treatment for intrathyroid papillary thyroid cancer

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Adapting treatment and follow-up according to the risk of recurrence and/or death from thyroid cancer is a relatively recent concept of “personnalized” medicine, developed particularly to avoid overtreatment of low-risk thyroid cancer which represents the majority of thyroid cancers diagnosed in the world today. For low-risk thyroid cancer, this decrease in extent of treatment involves the extent of surgery—total thyroidectomy, lobectomy or no surgery with active surveillance—but also the indications, doses and methods of stimulation when or if administering radioactive iodine (RAI), the indication for suppressive thyroxin therapy and the extent and modalities for follow-up that should be adapted to the risk of recurrence. The aim is to optimize medical resources and quality of life, particularly for low-risk patients whose life expectancy is that of the general population.



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## Introduction

Adapting treatment and follow-up according to the risk of recurrence and/or death from thyroid cancer is a relatively recent concept of "personnalized" medicine, developed particularly to avoid overtreatment of low-risk thyroid cancer which represents the majority of thyroid cancers diagnosed in the world today. For low-risk thyroid cancer, this decrease in extent of treatment involves the extent of surgery—total thyroidectomy, lobectomy or no surgery with active surveillance—but also the indications, doses and methods of stimulation when or if administering radioactive iodine (RAI), the indication for suppressive thyroxin therapy and the extent and modalities for follow-up that should be adapted to the risk of recurrence. The aim is to optimize medical resources and quality of life, particularly for low-risk patients whose life expectancy is that of the general population.

Although this risk-adapted treatment is promoted in recent guidelines, many of these treatment paradigms are based on retrospective studies and expert opinion, a weakness that is widely recognized by the authors and adherents of published guidelines [1,2]. Large cohorts or clinical trials are lacking. Future studies will allow for more precise calculations of recurrence rates according to treatment paradigms in more recent cohorts and will allow refinements in risk factors and the definition of risk groups.

## Notion of risk and definition of risk groups

### *Risk of death*

The AJCC/TNM staging system is currently most widely used and recommended for prognostication of the risk of death from thyroid cancer. The most recent 8th edition of the TNM classification, implemented on January 1st 2018, was designed to better reflect the excellent prognosis of most thyroid cancers in terms of disease-specific survival (Table 1) [3].(Microscopic extrathyroidal extension is no longer taken into account and no longer classified as T3, effectively downstaging these patients whose risk of recurrence may be higher (see below) but whose disease-specific survival remains excellent. Similarly, the presence of lymph node metastases alone no longer classifies older patients as stage III, and stage III is now comprised of older patients (>55 years) with gross extrathyroidal extension, with a higher risk of death from disease (Table 2).

The MACIS scoring system (presence of distant Metastases, patient Age, Completeness of resection, local Invasion, tumor Size) permits identification of groups of patients with different risks of dying from differentiated thyroid cancer. Twenty-year cause-specific survival rates for patients with MACIS scores of less than 6, 6 to 6.99, 7 to 7.99, and 8 + were 99%, 89%, 56%, and 27%, respectively ($p < .0001$).

**Table 1**
TNM 8th edition.

| **T - Primary Tumor** | **N − Regional Lymph Nodes** |
|---|---|
| T1a: intrathyroidal tumor ≤1 cm | Nx: regional lymph nodes cannot be assessed |
| T1b: intrathyroidal tumor >1 cm but ≤2 cm | N0a: no regional lymph node metastasis on cytology or pathology of at least one lymph node |
| T2: intrathyroidal tumor >2 but <4 cm | N0b: no regional lymph node metastases on palpation and ultrasound |
| T3a: intrathyroidal tumor ≥4 cm | N1a: metastases to the central compartment (level VI) and/or upper mediastinal lymph nodes (level VII) |
| T3b: tumor of any size with gross extrathyroidal extension invading strap muscles | N1b: metastases in other unilateral, bilateral or contralateral cervical lymph nodes (levels I, II, III, IV or V) or retropharyngeal lymph node |
| T4a: extrathyroidal extension with invasion of any of the following: subcutaneous soft tissues, larynx, trachea, oesophagus, recurrent laryngeal nerve | **M − Distant Metastases** |
| T4b: tumor invades prevertebral fascia, mediastinal vessels or encases carotid artery | M0: no distant metastases<br>M1: distant metastases |

**Table 2**
TNM stage grouping.

| Patients < 55 years of age | Patients 55 years of age and >55 |
|---|---|
| Stage I: any T, any N, M0 | Stage I: T1-T2, N0, M0 |
| Stage II: any T, any N, M1 | Stage II: T1-T2, N1, M0 and T3, any N, M0 |
| | Stage III: T4a, any N, M0 |
| | Stage IVA: T4b, any N, M0 |
| | Stage IVB: M1 |

When cumulative mortality from all causes of death was considered, approximately 85% of patients with MACIS scores below 6 had no excess mortality over rates predicted for control subjects in the general population [4]. Other scoring systems such as AMES (Age, Metastases, Extrathyroidal extension, tumor Size) and AGES (Age, tumor Grade, Extrathyroidal extension, Size) have similar survival profiles [5,6]. These staging systems are comparable to the TNM staging system in terms of predicting mortality. Due to the widespread use of the TNM classification in oncology in general, this classification is generally preferred over others to facilitate comparaisons and communication among centers [7].

Thus, the prognosis of intrathyroid differentiated thyroid carcinoma is generally excellent. Disease-specific survival at 20 years for the low risk group (T1T2N0) is estimated at 99% [8]. Patients <55 year old without distant metastases have an estimated 10-year disease-specific survival of 98–100%, versus 85–95% for those in the same age group with distant metastases. For patients >55 years, 10-year disease-specific survival is 98–100% for stage I disease, 85–95% for stage II, 60–70% for stage III and <50% for stage IV [3,9].

### *Risk of recurrence: ATA risk groups*

Given that the survival rate for non-metastatic thyroid cancers is excellent, the evaluation of the risk of recurrence has become the main measure of oncologic outcomes for these tumors and a means of tailoring treatment to avoid overtreatment of tumors with a low risk of recurrence. The most recent guidelines of the ATA have suggested risk-group staging according to the clinical and pathologic factors listed below (Table 3).

Unfortunately, several of these risk factors cannot be ascertained preoperatively and thus cannot guide the extent of initial surgery, leading to reoperative surgery in a certain number of cases treated initially by lobectomy [1,2]. They can be used, however, to guide indications for adjuvant RAI and for follow-up.

### *Ongoing risk stratification*

The observation that outcomes are also related to the response to treatment leads to the practical consideration that the initial risk grouping can be modulated according to this response. High-risk patient may have a complete response after therapy with no evidence of disease, and their risk of recurrence will ultimately be related to this response, even more than to their initial risk factors described above [10]. The definitions of excellent, biochemical incomplete, structurally incomplete and indeterminate responses to treatment (Table 4) are employed to re-classify patients into risk groups according to the risk of tumor recurrence once they have been treated.

One issue with using this risk grouping for precise prognostication is that the reported outcomes are based on retrospective studies and that the follow-up period in these studies may be inadequate. Recurrences occur late as compared to other solid tumors. In one large retrospective cohort study 77% of recurrences occurred within 5 years but the 23% remaining recurrences occurred later, between 5 and 8 years of follow-up [11]. Reliable rates of recurrence require studies with a long follow-up period. Furthermore, these studies report outcomes for historic cohorts that were treated more aggressively (and homogeneously) with total thyroidectomy and more often adjuvant RAI than what is being currently promoted [2]. Future studies will allow for more precise calculations of recurrence rates in more recent cohorts.

**Table 3**
American thyroid association risk grouping.

| ATA risk group | Tumor characteristics | Estimated risk of recurrence |
|---|---|---|
| Low risk papillary carcinoma | Intrathyroidal micropapillary carcinoma (uni or multifocal, including BRAFV600E mutated)[a]<br>Papillary carcinoma with *all* of the following characteristics:<br>- No local or distant metastases<br>- All macroscopic tumor has been resected<br>- No tumor invasion of loco-regional tissues or structures<br>- No aggressive histology<br>- No vascular invasion<br>- Clinical N0 or N1 with ≤5 micrometastases all <2 mm in largest dimension[a]<br>- No RAI-avid metastatic foci outside the thyroid bed on the first post-treatment whole-body RAI scan (if $^{131}$I is given)<br><br>Intrathyroidal, encapsulated follicular variant of papillary thyroid cancer[a] | ≤5% |
| Low risk follicular carcinoma | Intrathyroidal, well-differentiated follicular thyroid carcinoma with capsular invasion and <4 foci of vascular invasion[a] | |
| Intermediate risk | Papillary of follicular cancer with *any* of the following:<br>Microscopic invasion of perithyroid soft tissues<br>Aggressive histology<br>Papillary thyroid cancer with vascular invasion<br>Clinical N1 or >5 N1 all <3 cm in the largest dimension[a]<br>RAI-avid metastatic foci in the neck outside the thyroid bed on the first post-treatment whole-body RAI scan<br>Multifocal micropapillary cancer with extrathyroidal extension and BRAF V600E mutation (if known)[a] | 5–20% |
| High risk | Papillary of follicular cancer with *any* of the following:<br>Macroscopic invasion of perithyroid soft tissues and/or structures (gross extrathyroidal extension)<br>N1 with any metastatic node ≥3 cm in the largest dimension[a]<br>Incomplete tumor resection<br>Distant metastases<br>Follicular cancer with extensive vascular invasion (>4 foci)[a]<br>Postoperative serum thyroglobulin suggestive of distant metastases | >20% |

[a] Denotes factors that were added in the 2015 ATA guidelines, as compared to the previous ATA Guidelines published in 2009.

**Table 4**
Risk of recurrence according to response to therapy.

| Response to therapy category | Definition: patients treated with total thyroidectomy and RAI ablation | Expected risk of recurrence |
|---|---|---|
| Excellent response | Negative imaging<br>*And* Tg with Lthyroxin treatment <0.2 ng/mL *or* TSH-stimulated Tg < 1 ng/mL<br>*And* no thyroglobulin antibodies | <1–4% |
| Biochemical incomplete response | Negative imaging<br>*And* Tg with Lthyroxin treatment > or = 1 ng/mL<br>*Or* stimulated Tg > or = 10 ng/mL<br>*Or* rising thyroglobulin antibodies | May evolve spontaneously to excellent response<br>20% develop structural disease |
| Indeterminate response | Nonspecific findings on imaging<br>*And* basal Tg 0.2–1 ng/mL<br>*Or* stimulated Tg 1–10 ng/mL<br>*Or* stable or declining Tg antibodies over time | 15–20% will develop structural disease |
| Structural incomplete response | Evidence of disease on imaging | 100% |

In the seminal study defining ongoing risk stratification, low risk patients with an excellent response to therapy had a recurrence rate of 2% and high-risk patients with an excellent response had a recurrence rate of 14% (Table 5) [10].

The table below shows the rates for structural recurrent or persistent disease after further therapy for the patients in this study, in which the initial risk grouping was based on criteria from the ATA guidelines published in 2009 [12] as a function of the initial response to therapy. This data is particularly important by showing that many low risk patients (87%) will finally have no structural evidence of disease after further treatment. Furthermore, a biochemically incomplete or and indeterminate response may not necessarily lead to structural recurrence and that thyroglobulin levels may decline spontaneously over time.

## Risk-oriented extent of surgery

It is currently recommended that the extent of surgery be adapted to the individual patient's risk group: very low, low, intermediate or high.

### *"Very" low risk cancers*

"Very" low risk cancers may be defined as unifocal intrathyroidal micropapillary carcinoma (<or = 10 mm in diameter) with no suspicion of lymph node metastases or distant metastases [13]. Given the excellent prognosis for these tumors, a new "active surveillance" paradigm aiming to avoid surgery altogether has been developed and evaluated in several prospective registries studies, particularly from Japan. The largest study to date of 1235 patients undergoing active surveillance for asymptomatic unifocal micropapillary carcinoma with no lymph node metastases found that over a 10-year period, 8% of patients had tumor growth of more than 3 mm and 3.8% of patients had the appearance of metastatic lymph nodes [14,15]. Tumor growth was more prevalent in patients less than 40 years old: 9.1% at 5 years versus 5% for patients 40–50 years old and 4% for those >60 years old). De novo nodal metastases showed the same trend, with 5.2% of patients less than 40 having de novo lymph node metastases over a 5-year follow-up, versus 1.4% for patients 40–50 years old and 0.5% for those over 60. All patients who progressed were successfully treated with surgery, and no patient died of disease.

Similarly, Sugitani et al. reported a series of 244 patients, with a 7% incidence of tumor growth and a 1% incidence of de novo lymph node metastases over a mean 5-year follow-up period [16]. The same team found that TSH levels were not predictive of tumor growth in these patients [17] whereas a team from Korea found a correlation between tumor growth and high TSH levels (>2.5 mU/L) [18]. In a study of 291 patients from the USA, 12.1% of patients had tumor growth at 5 years [19]. One recent study, also from Japan, reports similar outcomes for selected intrathyroidal papillary carcinoma T1b, which remain to be confirmed in other centers [20].

The only systematically identified risk factors for tumor growth or the appearance of metastatic lymph nodes is age <40. Microcarcinoma adjacent to the trachea forming an obtuse angle with the tracheal cartilage are also at risk of tracheal invasion and may not be ideal candidates for active surveillance [15]. With this limited data, the ideal candidate for active surveillance appears to be an older

**Table 5**
Final risk of structurally recurrent/persistent disease as a function of initial ATA risk grouping (ATA 2009) and response after initial therapy.

| | Excellent response after 1st treatment sequence | Biochemical incomplete or indeterminate response | Structural incomplete response |
|---|---|---|---|
| ATA low risk | 2% | 0% | 13% |
| ATA intermediate risk | 2% | 0% | 41% |
| ATA high risk | 14% | 0% | 79% |

patient (>60 years old) with unifocal intrathyroidal mirocarcinoma at least 2 mm from the thyroid capsule with no evidence of nodal or distant metastases that can be followed up reliably in an experienced center with prospective data collection [21].(Table 6) Young patients (<18), micropapillary cancers located subcapsularly and posteriorly adjacent to the recurrent laryngeal nerve or with suspicion of extrathyroidal extension would generally be considered as inappropriate candidates for active surveillance [21].

For selected tumors, patients and physicians now have two treatment options for these very low risk cancers, but is active surveillance better for patients in terms of quality of life? Some patients may choose up-front surgery (lobectomy) instead of active surveillance, or eventually go on to have surgery due to personal anxiety even though the morbidity of surgery has been shown to be higher than that of active surveillance [22,23]. A survey study of 249 patients under active surveillance for thyroid cancer found that the cancer concern reduced over time in 60% of patients, and up to 25% reported to be “not at all worried” [24]. More thorough physician-, patient- and population-oriented education may help relieve some of this anxiety and lower the rate of up-front surgery in the future.

From a different perspective, however, a study from the USA calculated expected costs of lobectomy versus active surveillance and found that, for a model 40 year old patient, active surveillance may be actually more costly than up-front lobectomy [25], whereas Japanese and Chinese data show the contrary [26,27]. Again, more follow-up is needed to determine the role of active surveillance, the ideal patients and the rate of follow-up to optimize outcomes, quality of life and costs.

If surgery is chosen for these “very” low risk cancers, there is fairly high-level evidence from database studies showing that lobectomy alone without radioactive iodine treatment (RAI) is comparable to total thyroidectomy (without RAI) for unifocal intrathyroidal cN0 microcarcinoma (T1a, < or = 10 mm) [28]. in terms of overall survival and recurrence. The risk of loco-regional recurrence can be estimated at <1% and the risk of death from thyroid cancer essentially zero [14,29].

**Table 6**
Important characteristics when considering active surveillance for papillary microcarcinoma.

| Ideal situation | May be appropriate | Inappropriate |
|---|---|---|
| Solitary nodule with well-defined margins on ultrasound | Multifocal micropapillary carcinoma with no suspicion of extrathyroidal extension or posterior subcapsular location | Posterior subcapsular extension or suspicion of extrathyroidal extension |
| No suspension of extrathyroidal extension | Nodule with poorly defined margins | N1 disease initially or during active surveillance |
| Margin of normal thyroid tissue 2 mm or more | Other ultrasound findings (thyroiditis, other non-suspicious thyroid nodules, non specific lymph nodes) | Growth of tumor 3 mm or more |
| cN0cM0 | FDG avid tumor | Evidence of aggressive form on cytology |
| Previous ultrasound showing stability | Age 18-59 | Evidence of invasion of the recurrent nerve or trachea |
| Older patients (>60 years) | Strong family history of papillary thyroid cancer | Distant metatstases |
| Willing to submit to active surveillance (versus thyroid lobectomy) | Child bearing potential | Patients <18 years of age |
| Support from family, significant others and other healthcare providers | Experienced endocrinologist or thyroid surgeon | Patients not likely or not willing to comply with active surveillance |
| Life-threatening comorbidities rendering surgery less favorable | Routine ultrasonography available | Absence of physician familiar with thyroid cancer management |
| Follow-up by an experienced team with specialized ultrasonography | | Routine ultrasound not available |
| Reminder program to avoid patients lost to follow-up | | |
| Prospective data collection | | |

*Low risk cancers*

*Lobectomy versus total thyroidectomy*

For low risk, T1T2N0 differentiated thyroid cancer, several large database and retrospective studies have shown that survival is similar whether a lobectomy or a total thyroidectomy is performed as the initial treatment [28,30]. A large SEER (National Cancer Institute Database; Survival Epidemiology and End Results program) database study of 61,755 patients found no difference in survival between lobectomy and total thyroidectomy for unifocal intrathyroidal tumors 1–4 cm, N0 [28]. In a matched-pair analysis of 762 patients with tumors 1–4 cm with no lateral lymph node or distant metastases, 381 patients were treated with total thyroidectomy and 381 patients with lobectomy [30]. Disease-free survival was not different between the groups after a median follow-up of 9.8 years, and the rate of structural recurrent/persistent disease was not related to the extent of initial surgery. As a consequence, the current American Thyroid Association Guidelines provide the option of lobectomy for these low risk, unifocal intrathyroidal tumors 1–4 cm, with no evidence of lymph node metastases [1].

Thyroid lobectomy has the definite advantage of causing fewer surgical complications, even for experienced, high-volume surgeons [31,32]. The relative risks of permanent recurrent nerve paralysis, permanent hypoparathyroidism and postoperative hematoma after total thyroidectomy were 1.9, 3.2 and 2.6%, respectively, as compared to thyroid lobectomy [32]. And despite a high rate of completion thyroidectomy for these tumors 1–4 cm (see below) lobectomy still seems to be cost-effective as compared to up-front total thyroidectomy [33].

Still, 10–50% of patients will still require thyroid hormone supplementation after lobectomy due to the development of hypothyroidism [34–36], and up to 73% if the TSH level is to be maintained between 0.5 and 2 UI/L, as suggested in the 2015 ATA Guidelines [1,37]. Any advantage of maintaining at least a small amount of residual endogenous T3 after lobectomy has yet to be demonstrated.

Some risk factors such as aggressive histology, multifocality and vascular invasion are difficult to diagnose preoperatively. According to several studies, 43–59% of patients with tumors between 1 and 4 cm would potentially require completion lobectomy due to postoperative findings of intermediate-risk features not ascertained preoperatively [38–41].

Finally, even if overall and cause-specific survival for lobectomy and total thyroidectomy are comparable for selected low-risk patients, there seems to be a slightly higher risk of locoregional recurrence after lobectomy, namely the risk of recurrence on thyroid remnant that is <5%, that can be treated successfully [42–45]. The current ATA guidelines state: "Accepting a slightly higher risk of locoregional recurrence is a reasonable management strategy." [1].

*Prophylactic neck dissection*

Even for low risk cancers with no evidence of lymph node metastases, the rate of micrometastases found on systematic prophylactic neck dissection is particularly high, ranging from 35–70% [46]. Despite this high rate of occult lymph node metastases, the rate of regional recurrence even in the absence of prophylactic neck dissection is low, less than 10%. A recent meta-analysis including 23 studies with a total of 18,376 patients found a statistically significant difference in regional recurrence rates of 2.5% vs 4.6% (CI = 0.48–0.88) with prophylactic neck dissection for these low-risk tumors [47]. Even though the difference is significant, it is small in terms of the percentage of recurrences avoided by prophylactic neck dissection. Furthermore, a large meta-analysis of retrospective studies has demonstrated an increase in temporary hypoparathyroidism with prophylactic central neck dissection [48] although other studies fail to find a significant difference in terms of complications [49].

A prospective randomized study of 181 PTC patients with no clinical or sonographic evidence of lymph node metastases did not find any difference between thyroidectomy alone compared with thyroidectomy and prophylactic central neck dissection [50]. In this study, the patients treated with thyroidectomy alone received significantly more RAI treatments compared with those that had had prophylactic neck dissection but the indication for these treatments were not reported by the authors, and final interpretation of the results is difficult [50].

With these pros and cons in mind, the current ATA guidelines allow for each treatment team to choose their strategy, if the information gained from prophylactic central neck dissection would aid in further treatment decision-making [1]. Prospective randomized trials are needed to finally put this question to rest, and despite the high number of patients needed to achieve a sufficient level of statistical power [51], there are currently several active randomized controlled trials underway (see www.clinicaltrials.gov).

*Intermediate risk cancers*

Total thyroidectomy is recommended particularly to enable RAI administration as an adjuvant treatment with the goal to improve oncologic outcomes, as suggested by some retrospective studies [1,10,52]. Microscopic extrathyroidal extension (ETE) is associated with an increased risk of lymph node metastases and thus ultimately (in theory) with an increased risk of neck recurrence [53,54]. This risk, however, is not ultimately associated with a increased risk of death, as has been shown by several studies comparing patient outcomes using the newest 2017 TNM classification in which microscopic ETE does not upstage patients versus the previous 2010 classification in which tumors with ETE were classified as T3 [3]. Thus, total thyroidectomy aims to improve recurrence rates for this risk group and facilitate follow-up (see below).

*High-risk cancers*

Some intrathyroidal cancers—with no invasion of strap muscles or other regional structures—may still be classified in the high-risk group with vascular invasion, large lymph node metastases and/or distant metastasis. Experts and guidelines still agree upon the need for total thyroidectomy and high-dose RAI to optimize oncologic outcomes for these tumors [1,55].

## Risk-oriented radioactive iodine therapy

The administration of radioactive iodine (RAI), which may be performed only after a total or near-total thyroidectomy, has several objectives:

- Eliminate normal thyroid tissue (thyroid remnant ablation) to ensure that subsequent thyroglobulin measurements reflect only persistent/recurrent thyroid cancer
- Perform a whole-body scintigraphy (often coupled with a CT scanner in the form of a SPECT-CT)
- Theoretically decrease the risk of recurrent disease
- Treat residual disease in the neck or distant metastases
- Locate recurrent disease in case of an increase in serum thyroglobulin or anti-thyroglobulin antibodies during follow-up.

The dose of RAI (or activity in Becquerels, Bq, or millicuries, mCi) and the method of increasing TSH levels to stimulate the uptake of iodine by the thyroid tumor cells varies according to the desired objective. Furthermore, in many cases for low-risk thyroid cancer today, the risks and disadvantages seem outweigh the potential advantages, and systematic RAI is no longer the norm (Table 7).

The symptoms of thyroid hormone withdrawal—fatigue, weight gain, edema, depression and non-specific biochemical abnormalities—are well known and are a major drawback to RAI therapy. When indicated, using recombinant TSH instead of thyroid hormone withdrawal avoids the temporary adverse effects of thyroid hormone withdrawal [55].

In terms of toxicity, RAI is generally well-tolerated, but may cause acute radiation gastritis leading to temporary nausea and vomiting. Acute inflammation of the salivary glands (sialadenitis) due to the accumulation of iodine in saliva causes swelling, pain and dysgeusia or ageusia. The parotid glands are the most often affected and symptoms may be uni- or bilateral. These symptoms usually resolve spontaneously in several days or weeks. Other acute effects concern fertility with an increased rate of miscarriages and a temporary decrease in sperm count. Pregnancy and lactation are contra-indications to RAI and pregnancy should be avoided for 6–12 months following treatment. High cumulative activities of RAI have been correlated with subsequent male infertility and male patients should be counselled and sperm banking proposed for patients likely to receive repeated doses of $^{131}I$ [1].

**Table 7**
Tumor characteristics susceptible to guide use of RAI administration.

| ATA risk group | Specific characteristics | Evidence for improvement in disease-specific survival | Evidence for improvement in disease-free survival | Indication for postsurgical $^{131}I$ |
|---|---|---|---|---|
| Low risk | Tumor < or = 10 mm<br>Uni or multifocal | No | No | No |
| | T1bT2 N0Nx | No | Conflicting data[a] | Not routine, may be considered on a case by case basis, 30–100 mCi with rhTSH |
| Low/ intermediate risk | Tumor >4 cm | Conflicting data | Conflicting data | May be considered<br>30–100 mCi with rhTSH |
| | Microscopic extrathyroidal extension | No | Conflicting data | Generally favored<br>30–100 mCi with rhTSH (unless other unfavorable characteristics) but may not be needed for small tumors |
| | N1a | Possibly for patients 45 years or older | Conflicting data | Generally favored<br>Dose and method of stimulation according to number and size of lymph node metastases |
| | N1b | Possibly for patients 45 years or older | Conflicting data | Generally favored<br>Dose and method of stimulation according to number and size of lymph node metastases |
| High risk | Gross extrathyroidal extension | Yes | Yes | Yes<br>High doses of RAI and thyroid hormone withdrawal |
| | Distant metastases | Yes | Yes | Yes<br>High doses of RAI and thyroid hormone withdrawal |

[a] Prospective randomized studies are currently underway.

Late effects include chronic sialadenitis, which is not related to the occurrence of acute sialadenitis. The pain, swelling and xerostomia are related to salivary duct stenosis. The symptoms generally resolve within 1 year with subsequent atrophy of the salivary glands. The xerostomia may lead to dental problems. Ocular dryness and lacrymal duct stenosis do not seem to be dose related and should be managed by specialists [56–59].

Finally, second primary cancers—colon, breast, salivary, kidney, leukemia and bone or soft tissue tumors—have been shown to be more frequent in patients having received RAI, but with a low overall relative risk of 1.19. The risk is higher in patients receiving a higher cumulative dose. For low single doses, there is no direct evidence of a significant risk of second primary malignancies, however [1,60]. Colon irradiation should be mitigated by laxative treatment, and bladder irradiation by abundant hydration and frequent urination during treatment.

### *Very low risk cancers*

For papillary thyroid microcarcinoma with no adverse characteristics, thyroid lobectomy or active surveillance may be proposed, and RAI is not recommended.

### *Low risk cancers*

High-level evidence from 2 prospective randomized trials show that for low-risk tumors low-dose RAI (1.1 GBq or 30 mCi) with injectable recombinant human TSH stimulation (versus thyroid hormone withdrawal) is sufficient for thyroid remnant ablation [61,62]. In terms of risk of recurrence in this patient group the prospective data from one of these studies found that 3- 5- and 7-year cumulative recurrence rates were not statistically different between patients treated with low- or high-dose RAI nor between patients treated with rhTSH versus thyroid hormone withdrawal [63]. Recurrence rates for the low- and high-dose groups were 1.5 vs 2.1% respectively at 3 years, 2.7 vs 2.7% respectively at 5 years and 5.9 vs 7.3% respectively at 7 years. Recurrence rates were similar to these figures when comparing the rhTSH group with the thyroid hormone withdrawal group, with no significant difference between the groups. In the other prospective randomized trial, after a median follow-up of 5.4 years, 11/726 patients (1.5%) were found to have a "not-excellent" response (structural, biochemical or indeterminate responses), 6 in the low-dose groupe and 5 in the high-dose group [61,64]. There were no thyroid cancer related deaths in either study.

Thus, for low-risk differentiated thyroid cancer low-dose RAI is equivalent to a high-dose and rhTSH may be safely used instead of thyroid hormone withdrawal, But is RAI administration really necessary for low-risk patients, due to such low recurrence rates? In the current ATA guidelines, RAI administration is not recommended in routine for low-risk patients but "may be considered" and it is recommended to use rhTSH.(ATA) Prospective randomized clinical trials are currently underway to definitively answer the question or the need for RAI following surgery in these low-risk patients (www.clinicaltrials.gov).

*Intermediate risk cancers*

One of the prospective randomized trial comparing low- and high-dose RAI included 147 patients in the ATA intermediate risk group: 70 received low-dose RAI and 77 a high-dose, but even for these intermediate-risk patients, the recurrence rate was not significantly different between the groups, with a 7-year recurrence rate of 7.1 in the former group and 9.1 in the latter ($p = .67$) [62]. Thus for some intermediate risk patients, low dose RAI with rhTSH is an acceptable method of treatment (see table below) [1].

*High risk cancers*

Radioactive iodine therapy is generally recommended for high-risk cancers, with preferentially higher doses and endogenous stimulation after thyroid hormone withdrawal.

## Risk-oriented thyroid hormone suppression therapy

The objective of thyroid hormone suppression—administering thyroid hormone orally so that TSH levels are below the normal range or undetectable—is to slow growth of thyroid tumor cells and, in theory, to lower rates of recurrence and/or mortality. Retrospective and cohort studies have found that TSH suppression to undetectable levels improved overall survival in patients with stage III-IV cancer, and suppression to low or undetectable levels had the same effect in patients with stage II disease, but no difference was found for stage I cancer [65].

The risks of long term thyroid hormone suppression are the same as those of hyperthyroidism, and include heart arrhythmia, exacerbation of symptoms of coronary artery disease, osteoporosis and psychic side effects. These risks and individual patients' cardiac and bone risk factors need to be put in the balance as relates to the oncological benefit of thyroid hormone suppression.

*Very low risk and low risk patients, patients with an excellent response*

There is no evidence that thyroid hormone suppression improves recurrence rates or survival in these patients once an excellent response has been obtained. In theory, however, high TSH levels should be avoided, and the current ATA guidelines suggest maintaining the TSH level within the normal range but below or up to 2 mU/L. TSH suppression will not decrease the already low recurrence rate but may cause adverse effects such as cardiac arrhythmia, osteoporosis, anxiety/nervousness or insomnia.

For patients with an indeterminate response, TSH suppression to a range between 0.1 and 0.5 mU/L is suggested. For patients with a biological incomplete response or with persistent/recurrent structural disease, TSH suppression below 0.1 mU/L is recommended in the absence of cardiac and bone risk factors.

After lobectomy a goal TSH 0.5–2 is recommended, but based on low level evidence. (ATA) As seen above, however, up to 73% of initially euthyroid patients may need thyroid hormone replacement therapy after lobectomy if this level is to be maintained [37].

In active surveillance protocols for very low risk papillary thyroid microcarcinoma, TSH values should be maintained in the normal range, with thyroid hormone supplementation if necessary [21]. Due to the fact that some studies have suggested a correlation between tumor growth and higher TSH levels [18], some groups give patients the option of mild thyroid hormone suppression with the hypothesis of slowing tumor progression [66].

### *Intermediate risk patients*

Initial TSH suppression within the range of 0.1–0.5 mU/L is recommended for intermediate risk patients [1]. There is a lack of objective data to substantiate this recommendation, however, and the recommendation level is “weak” in the ATA guidelines. For patients achieving a durable excellent response, limiting TSH suppression to the 0.5–2mU/L range may be considered.

### *High risk patients*

For high risk patients, thyroid hormone suppression with TSH levels below 0.1 mU/L are generally recommended, with modulation according to response to initial therapy and according to individual patients' cardiac and bone risk factors [1].

## Risk-oriented follow-up

For follow-up, the types of exams and their frequency should be adapted to the risk group, the type of recurrence that may be expected (loco-regional or metastatic) and the response to initial therapy (Table 8) [67].

### *Serum thyroglobulin*

Serum thyroglobulin (Tg) is the most sensitive means of determining disease-free status for differentiated thyroid cancer. After total thyroidectomy and RAI ablation, for low and intermediate risk patients, if serum Tg is low or undetectable (ultrasensitive Tg, usTg<0.2 ng/mL if measured under levothyroxine and Tg < 1 ng/mL if measured after TSH stimulation) without Tg antibodies and if neck ultrasound is normal, the subsequent risk of recurrence is estimated at <2%. In these patients, ultrasound should not be repeated annually, but at a longer interval, as long as annual Tg measurements remain low in the absence of Tg antibodies, due to the high rate (8–67%) of false positive images on routine neck ultrasound [67]. Even though the rate of recurrence for these patients is very low, patients should not be lost to follow-up due to the fact that recurrent disease in low-risk patients tends to appear after a long delay of 5–8 years [11].

After total thyroidectomy without RAI, if the postoperative Tg is low or undetectable and in the absence of Tg antibodies, it can be used for follow-up as above. If the usTg level is above 0.2 ng/mL, Tg and Tg antibodies should be serially measured to ensure that the level remains stable over time. A rising Tg above 0.2 ng/mL, a rising level of Tg antibodies or the detection of previously-undetectable Tg antibodies should alert the clinician to the possibility of recurrent disease and eventually lead to consider RAI administration and whole-body scintigraphy.

After lobectomy, there is a paucity of data with long follow-up defining a fixed limit for Tg values that may be correlated to the presence or absence of recurrent disease. Retrospective studies have set a cutoff value at 30 ng/mL [45], but other studies suggest that after lobectomy, thyroglobulin levels tend to increase in all patients, and may not be sensitive enough for detection of recurrent disease in the contralateral lobe or in lymph nodes [68]. More data is needed to orient follow-up after lobectomy based on Tg levels.

**Table 8**
Follow-up strategies according to the response to therapy category.

| Response to therapy category | Definition: patients treated with total thyroidectomy and RAI ablation | Expected risk of recurrence | Proposed definition: patients treated with total thyroidectomy *without* RAI ablation | Proposed definition: patients treated with thyroid lobectomy | Management implications | Proposed schedule (based on authors opinion) |
|---|---|---|---|---|---|---|
| Excellent response | Negative imaging<br>*And* Tg with Lthyroxin treatment <0.2 ng/mL *or* TSH-stimulated Tg < 1 ng/mL<br>*And* no thyroglobulin antibodies | <1–4% | Negative imaging<br>*And* Tg with Lthyroxin <0.2 ng/mL *or* TSH-stimulated Tg < 2 ng/mL<br>*And* no thyroglobulin antibodies | Negative imaging<br>*And* Tg < 30 ng/mL<br>*And* no thyroglobulin antibodies | Should lead to decreased intensity and frequency of follow-up and less TSH suppression (TSH 0.5–2 ng/mL) | Very low/low risk treated with lobectomy alone<br>Neck US (±Tg and thyroglobulin antibodies) every 5 years<br>Low risk treated with total thyroidectomy<br>Neck US + Tg and thyroglobulin antibodies every 2–3 years<br>Intermediate/high risk<br>Tg and thyroglobulin antibodies every 12–24 months |
| Biochemical incomplete response | Negative imaging<br>*And* Tg with Lthyroxin treatment > or = 1 ng/mL<br>*Or* stimulated Tg > or = 10 ng/mL<br>*Or* rising thyroglobulin antibodies | May evolve spontaneously to excellent response 20% develop structural disease | Negative imaging<br>*And* basal Tg > 5 ng/mL<br>*Or* stimulated Tg > 10 ng/mL<br>*Or* rising Tg levels over time with stable TSH<br>*Or* rising thyroglobulin antibodies | Negative imaging<br>*And* basal Tg > 30 ng/mL<br>*Or* rising Tg levels over time with stable TSH<br>*Or* rising thyroglobulin antibodies | Tg stable or declining: continued observation<br>Tg or Tg antibodies rising: consider additional investigation and therapy | Low risk:<br>Tg and thyroglobulin antibodies every 24 months<br>Neck Us after 3–5 years then every 5 years<br>Intermediate/high risk<br>Tg and thyroglobulin antibodies + neck US every year<br>If rising trend FDG PET ±cross sectional imaging |
| Indeterminate response | Nonspecific findings on imaging<br>*And* basal Tg 0.2–1 ng/mL<br>*Or* stimulated Tg 1–10 ng/mL<br>*Or* stable or declining Tg antibodies over time | 15–20% will develop structural disease | Nonspecific findings on imaging<br>*And* basal Tg 0.2–5 ng/mL<br>*Or* stimulated Tg 2–10 ng/mL<br>*Or* stable or declining Tg antibodies over time | Nonspecific findings on imaging<br>*And/or* stable or declining Tg antibodies over time | Continued observation with repeated imaging of nonspecific lesions and Tg monitoring | Low risk:<br>Tg and thyroglobulin antibodies every 24 months<br>Neck Us after 3–5 years then every 5 years<br>Consider more frequent imaging in patients with persistently high titres of antithyroglobulin antibodies<br>Intermediate/high risk<br>Tg and thyroglobulin antibodies + neck US every year |
| Structural incomplete response | Evidence of disease on imaging | 100% | Evidence of disease on imaging | Evidence of disease on imaging | Additional treatment or observation (depending on lesion size, location, growth rate, RAI/$^{18}$FDG avidity, pathology subtype) | Tg and thyroglobulin antibodies + imaging at least every 6–12 months |

*Neck ultrasound*

A neck ultrasound (US) should be performed in all patients 6–18 months after RAI administration (or after surgery alone), to determine the type of response to therapy. After that, the rhythm at which neck ultrasound should be repeated is not clearly defined. It should be adapted to the risk of recurrence based on Tg and Tg antibody levels, ATA initial risk stratification, TNM classification, and response to therapy. In low risk patients with an excellent response (see table) it is suggested that follow up with neck US is not necessary until 3–5 years after the initial treatment [67]. Intermediate risk patients with an excellent response may benefit from a routine neck ultrasound at a more frequent interval (12–24 months), whereas in high risk patients it is suggested to perform neck US every 6–12 months. Of course, biological suspicion of recurrence should prompt earlier neck US and/or other types of imaging.

Inasmuch as the response to therapy seems to be the most sensitive criteria for determining the risk of recurrence, it is currently suggested that follow-up be tailored to the response to therapy, as outlined in the table below. A high level of caution should be maintained, however, for patients initially in th high-risk category.

## Conclusions

Risk-oriented treatment and follow-up has been developed with the aim to avoid overtreatment while maintaining a low rate of mortality and recurrence for the vast majority of thyroid cancers that are in the very low-, low- and intermediate-risk groups. Further prospective, well-structured studies are needed to refine these risk groups, define new risk factors and in particular molecular factors, and provide reliable statistics on outcomes. Hopefully this strategy will improve patients' quality of life and lower individual and collective costs of treating low-risk thyroid cancer, while maintaining vigilant treatment and follow-up for the rarer aggressive cancers.

## Summary

Modern treatment of differentiated thyroid cancer is based on a thorough knowledge of different risk classifications and adapted to optimize the risk/benefit ratio of surgery, radioactive iodine and follow-up. Highly selected micropapillary thyroid carcinoma are now considered to be amenable to active surveillance in specialized centers with no added risk of deleterious oncologic events, and in the future this approach will be evaluated with regards to larger, selected low-risk cancers. More data is need to objectify the costs and quality of life issues of surveillance versus surgery very low risk cancers. Lobectomy may be adequate for selected patients with low-risk tumors, and further studies including molecular analysis in particular may in the future aid in optimizing patient selection for less treatment. Radioactive iodine today is administered according to a large number of risk factors for tumor recurrence and for low risk tumors is no longer routinely recommended. For most intermediate and high risk tumors, total thyroidectomy combined with radioactive iodine is still the recommended treatment.

**Practice Points**

- Modern treatment of differentiated thyroid cancer is based on a thorough knowledge of different risk classifications and adapted to optimize the risk/benefit ratio of surgery, radioactive iodine and follow-up
- Highly selected micropapillary thyroid carcinoma are now considered to be amenable to active surveillance in specialized centers with no added risk of deleterious oncologic events
- Selected very low and low-risk cancers may be treated with thyroid lobectomy alone, but criteria for follow-up with thyroglobulin levels need to be refined by future studies
- For most intermediate and high risk tumors, total thyroidectomy combined with radioactive iodine is still the recommended treatment

**Research Agenda**

- Further studies are needed to evaluate costs and quality of life for patients eligible for active surveillance of micropapillary thyroid cancers
- Active surveillance may also be adequate for larger, highly selected papillary cancers in selected patients, but further studies are needed
- Further studies are needed to optimize and homogenize follow-up practices for low-risk cancers
- Prospective randomized studies are currently underway to definitively resolve the question of prophylactic central neck dissection for low-risk cancers

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