

REVIEW

An update on the management of low-risk differentiated thyroid cancer

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Abstract

Low-risk papillary cancers, which represent the vast majority of thyroid cancers diagnosed today, do not require aggressive treatment or follow-up. Initial treatment consists of a total thyroidectomy without prophylactic lymph node dissection. A hemithyroidectomy is an alternative in some patients with an intrathyroidal tumor and with a normal contralateral lobe at pre-operative neck ultrasonography. The use of post-operative radioiodine should be restricted to selected patients. Follow-up at 6–18 months is based on serum thyroglobulin (Tg), Tg-antibody determination and neck ultrasonography. In the absence of any abnormality (excellent response to treatment), the risk of recurrence is extremely low and follow-up may consist of serum TSH monitoring that is maintained in the normal range, and a Tg and Tg-antibody titer determination every year. There is no need for referral to a specialized center. In patients with detectable serum Tg or detectable Tg antibodies, the trend over time of these markers on levothyroxine treatment will dictate subsequent follow-up: a decreasing trend is reassuring, but an increasing trend should lead to imaging, starting with neck ultrasonography.

Key Words

- ▶ low-risk thyroid cancer
- ▶ total thyroidectomy
- ▶ hemithyroidectomy
- ▶ thyroglobulin
- ▶ neck ultrasonography
- ▶ radioactive iodine

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Introduction

Differentiated thyroid carcinoma (DTC) accounts for more than 90% of all thyroid cancers (Lamartina *et al.* 2018a). Over the last decades, an increasing incidence of DTC has been reported in many countries (McLeod *et al.* 2013). This increase is largely due to an increased detection of small papillary thyroid cancers (PTC), as a result of the widespread use of neck ultrasound (neck-US) and fine-needle aspiration cytology (Vaccarella *et al.* 2016). Over 80% of thyroid carcinomas currently diagnosed are PTC with an excellent long-term prognosis (Durante *et al.* 2010, 2013a).

A one-size-fits-all approach used to be the treatment paradigm for DTC. It included total thyroidectomy and post-operative administration of a high activity of radioactive iodine (RAI) followed by suppressive levothyroxine therapy (Mazzaferrri & Jhiang 1994).

This type of aggressive strategy is still appropriate for high-risk DTCs (Berdelou *et al.* 2018, Grani *et al.* 2018), but for the vast majority of tumors currently diagnosed that have a low risk of mortality and of recurrence, there is no convincing evidence that aggressive treatment is beneficial (Hay *et al.* 2018). Consequently, the current trend is toward the use of a more limited approach for these tumors, which still permits a reliable follow-up (Lamartina *et al.* 2018a).

Definition of low-risk patients

Pathological classification

PTC is the most common DTC histotype and most of the evidence used to determine the guidelines for the treatment of DTC relies on populations constituted exclusively or predominantly by PTCs.

Follicular thyroid cancer (FTC) and Hürthle cell thyroid cancer (HCC) represent about 6% of all DTCs (Lamartina *et al.* 2017b) and are considered to carry a worse prognosis compared to PTC (Grani *et al.* 2018) even if the diagnostic criteria for each of these types of carcinoma have changed several times in last decades (Tallini *et al.* 2017). The fourth edition of the World Health Organization Classification of Tumours (Lloyd *et al.* 2019) defines FTC and HCC as separate entities due to their different biological behavior and molecular profile (Ganly *et al.* 2013).

Risk of death from thyroid cancer

The global mortality rate from thyroid cancer is low (<2% at 5 years) (Tuttle *et al.* 2017). The risk of mortality from DTC is usually estimated using the American Joint Committee on Cancer and Union Internationale Contre le Cancer (AJCC/UICC) tumor node metastasis staging system. The eighth edition, introduced several changes to the seventh edition that aimed at improving our ability to identify the limited number (5–10%) of DTC patients who are at a substantial risk of dying from their cancer and in whom the majority of cancer-related deaths occur (i.e. stage III and IV patients) (Tuttle *et al.* 2017). The majority (90–95%) of DTC patients are classified as stage I or II and have a low risk of cancer-related death (<1%). In the eighth edition, the age threshold for increased risk of mortality was raised from 45 to 55 years. Therefore, a larger proportion of tumors are now classified as stage I or II based only on the absence or the presence of distant metastases, respectively (Lamartina *et al.* 2017c). In the eighth edition, tumors smaller than 4 cm that are

associated with microscopic extrathyroidal extension to the perithyroidal soft tissues are no longer classified as pT3 and are now classified according to their size as pT1 (up to 2 cm) or pT2 (2–4 cm). Furthermore, tumors with lymph node metastases in the central and lateral compartments have been downgraded from stage III to stage II.

The adoption of the eighth edition of the tumor node metastasis system is expected to result in the down-staging of approximately one-third of DTC patients (Lamartina *et al.* 2017c), and the superior accuracy of this new system for the prediction of disease-related mortality has been confirmed in several retrospective series (Kim *et al.* 2017, van Velsen *et al.* 2018).

The tumor node metastasis stage was designed exclusively for mortality prediction. However, the risk of thyroid cancer recurrence for any stage can be either low, intermediate or high (Lamartina *et al.* 2017c).

Risk of thyroid cancer recurrence

The risk of persistent or recurrent DTC is far more common than the risk of cancer death. The American Thyroid Association (ATA) risk-stratification system classifies the likelihood of persistent and/or recurrent disease as low (<5%), intermediate (5–20%), or high (>20%) based on features documented at the time of diagnosis (Table 1) (Haugen *et al.* 2016). These estimates of persistent and recurrent DTC rely mainly on retrospective data and can vary widely between studies.

PTCs with low and intermediate risks of recurrence represent the majority of patients (57 and 38%, respectively) in contemporary series (Lamartina *et al.* 2017b).

Table 1 Risk of recurrence according to 2015 American Thyroid Association guidelines.

Low	Intermediate	High
<ul style="list-style-type: none"> – No evidence of distant metastases – Intrathyroidal tumor; absence of macroscopic extra-thyroid extension – No evidence of clinically evident lymph node metastases – Clinically N0 or presence of ≤5 microscopic (<2 mm) lymph node metastases – No evidence of aggressive histology – No evidence of vascular invasion in papillary thyroid cancer – No evidence of incomplete macroscopic tumor resection – No uptake outside the thyroid bed on post-therapeutic whole-body scan (in patients treated with radioiodine) – Well-differentiated follicular thyroid cancer with capsular invasion only or less than four foci of vascular invasion 	<p>Any of the following criteria:</p> <ul style="list-style-type: none"> – Evidence of microscopic invasion into perithyroidal soft tissue – Aggressive histology – Papillary thyroid cancer with vascular invasion – Clinical lymph node metastases or more than five lymph node metastases with all lymph nodes <3 cm. – Uptake in the neck, outside the thyroid bed, on post-treatment whole-body scan – Multifocal papillary microcarcinoma with extra-thyroid extension and BRAFV600E mutation if known 	<p>Any of the following criteria:</p> <ul style="list-style-type: none"> – Evidence of distant metastases – Evidence of macroscopic invasion of perithyroidal tissue/structures – Evidence of lymph node metastases ≥3 cm – Follicular thyroid cancer with extensive vascular invasion (>4 foci) – Evidence of incomplete tumor resection – Serum thyroglobulin suggestive of distant metastases

PTCs ≤ 10 mm in maximum diameter, unifocal, intrathyroidal and with no aggressive histologic features have a very low risk of recurrence ($<1\%$) (Durante *et al.* 2010). The risk for recurrence associated with the presence of metastatic lymph nodes has been refined. The number of metastatic lymph nodes (<5 or ≥ 5), their size (≤ 2 mm, >2 mm or ≥ 3 cm), the number of lymph node metastases with extracapsular invasion (≥ 3 or <3) (Leboulleux *et al.* 2005) and probably their location (central versus lateral compartments) should be considered for recurrence estimates (Randolph *et al.* 2012). Minimal extrathyroidal extension has little impact on disease recurrence when no other risk factors (such as lymph node metastases) are present (Tam *et al.* 2018).

The molecular profile of the tumor may play a role in risk stratification (Haugen *et al.* 2016). *BRAFV600E* mutation alone is not an independent risk factor for PTC recurrence but in association with other clinicopathologic features such as minimal extrathyroidal extension and multifocality, it may identify a subset of PTC with increased risk of recurrence compared with *BRAF* wild-type tumors (Niemeier *et al.* 2012). The presence of *TERT* promoter mutation is associated to a poor prognosis in both PTC and FTC (Liu & Xing 2016) and tumors harboring a *TERT* mutation are considered at high risk of recurrence (Haugen *et al.* 2016).

According to the presence and extent of vascular and tumor capsule invasion, FTC is classified as minimally invasive (true MIFTC), minimally invasive with limited vascular invasion (or moderately invasive FTC) and widely invasive follicular carcinoma (WIFTC). True MIFTC with capsular invasion alone has a low risk of recurrence ($\leq 5\%$). The presence of angioinvasion increases the probability of distant metastases and tumor recurrence (Ito *et al.* 2013, Kim *et al.* 2014). Moderately invasive FTC with vascular invasion may be considered to carry an intermediate risk of recurrence (Grani *et al.* 2018), while WIFTC are at high risk (Haugen *et al.* 2016).

Dynamic risk assessment

The initial estimate of the risk of recurrence should be reevaluated at each follow-up according to the patient's response to treatment (Table 2) (Haugen *et al.* 2016). The response to treatment is usually assessed for the first time at 6–18 months after the initial treatment and is based on serum thyroglobulin (Tg) and anti-thyroglobulin antibody (TgAb) measurements and on imaging (namely neck-US). If the imaging study reveals persistent tumor foci, the patient's response to treatment is classified as structurally incomplete. If the imaging examination is negative, the response to treatment is classified as excellent if serum Tg and TgAb are

Table 2 Responses to treatment.

	Excellent response	Indeterminate response	Biochemical incomplete response	Structural incomplete response
Definition (2015 American Thyroid Association guidelines) ^a after total thyroidectomy and post-operative radioactive iodine administration	No evidence of structural disease on imaging AND Tg on LT4 <0.2 ng/mL OR stimulated Tg <1 ng/mL AND no TgAb	Nonspecific findings on imaging AND/OR Tg on LT4 ≥ 0.2 – <1 ng/mL OR stimulated Tg ≥ 1 – <10 ng/mL OR stable or declining TgAb titers	No evidence of structural disease on imaging AND Tg ≥ 1 ng/mL on LT4 OR stimulated Tg ≥ 10 ng/mL OR rising TgAb titers	Evidence of structural disease on imaging
Risk of structural recurrence (%)	<1 – 4	5 – 20	20	100
Proposed definition for patients treated with total thyroidectomy alone ^{b,c}	No evidence of structural disease on imaging AND Tg on LT4 <1 ng/mL AND no TgAb	Nonspecific findings on imaging AND/OR Tg on LT4 ≥ 1 – <2 ng/mL OR stable or declining TgAb titers	No evidence of structural disease on imaging AND Tg on LT4 >2 ng/mL OR rising Tg values with comparable TSH levels OR rising TgAb titers	Evidence of structural disease on imaging
Proposed definition for patients treated with hemithyroidectomy alone ^{b,c}	No abnormal finding on imaging AND low Tg on LT4 stable over time AND no TgAb	Nonspecific findings on imaging AND/OR stable or declining TgAb titers	No abnormal finding on imaging AND high Tg on LT4 OR rising Tg values over time with comparable TSH levels OR rising TgAb titers	Evidence of structural disease on imaging

^aHaugen *et al.* (2016); ^bMomesso *et al.* (2016). ^cThese thresholds have not been validated on wide independent series yet. A threshold of 30 ng/mL corresponding to half of the upper limit of the normal range has been proposed for patients who underwent a hemithyroidectomy, but this is still debated. LT4, levothyroxine; TgAb, anti-thyroglobulin antibodies; Tg, thyroglobulin.

undetectable. The response is indeterminate if the serum Tg level is low but not undetectable, and biochemically incomplete if the serum Tg level is high (for cutoff values see Table 2) (Haugen *et al.* 2016, Momesso *et al.* 2016).

Most recurrences will occur in patients with some evidence of persistent disease after the initial treatment, that is a non-excellent response. A response that is classified as excellent means that the risk of recurrence in patients initially classified as low risk is virtually zero. In patients initially classified as intermediate risk (Haugen *et al.* 2016), after an excellent response the risk falls to 1–2% indicating that a ‘soft’ follow-up may then be appropriate. Patients at high risk of recurrence at diagnosis but who have an excellent response to treatment have a low recurrence rate in some reports, but other studies found a substantial risk of recurrent disease, up to 14% (Vaisman *et al.* 2011). In patients already treated for a recurrence, whatever their initial risk classification, the risk of further recurrences is even higher at 25% (Lamartina *et al.* 2017a).

This review is aimed at highlighting the strengths and weaknesses of the initial treatment and follow-up strategies used in low-risk patients.

New paradigms for initial treatment of low-risk patients

Management options now include active surveillance for selected very low-risk tumors (Leboulleux *et al.* 2016). For low-risk patients, less extensive surgery is performed (e.g. total thyroidectomy with no prophylactic lymph node dissection or hemithyroidectomy) and the use of RAI remnant ablation after total thyroidectomy is selective, being performed only in the few patients with a significant risk of persistent or recurrent disease.

Surgery

Traditionally, the recommended surgical procedure for low-risk thyroid cancer was a total thyroidectomy. Papillary thyroid carcinoma may be multifocal and bilateral, and for this reason, total thyroidectomy might slightly decrease the risk of recurrence in the contralateral lobe. It also permits post-operative RAI ablation and permits an accurate follow-up with serum Tg measurements, even when RAI ablation has not been performed. However, total thyroidectomy has a higher morbidity (vocal nerve palsy and hypoparathyroidism) (Hauch *et al.* 2014) and does not decrease the mortality rate in low-risk patients as compared to hemithyroidectomy (Adam *et al.* 2014).

For these reasons, hemithyroidectomy might be considered as an alternative to total thyroidectomy in

low-risk patients with a thyroid tumor less than 4 cm, no evidence of extra-thyroid extension or of lymph node involvement and with a normal contralateral lobe on pre-operative neck-US (Haugen *et al.* 2016). Furthermore, hemithyroidectomy is indicated only in patients in whom there will be no indication for post-operative RAI ablation (Haugen *et al.* 2016). Another advantage is that after hemithyroidectomy, post-operative TSH level will remain within the normal range in two-thirds of patients for whom levothyroxine treatment might be omitted (Sugitani & Fujimoto 2010, Zatelli *et al.* 2018). The presence of *BRAFV600E* mutation is associated with tumor multifocality, minimal extrathyroidal extension and lymph node metastases (Xing 2007, Tallini *et al.* 2015); nonetheless, the presence of *BRAFV600E* mutation is not a contraindication to hemithyroidectomy in low-risk patients as previously defined (Haugen *et al.* 2016).

Therapeutic lymph node dissection is indicated when there is pre-operative evidence of lymph node metastases, but these patients are then not considered low risk. Prophylactic lymph node dissection of the central neck (i.e. dissection performed in the absence of evidence of lymph node involvement) has not been demonstrated to decrease the risk of recurrence in these low-risk patients and slightly increases the risk of morbidity (hypocalcemia) even when performed by a skilled surgeon and therefore is usually not recommended in these patients (Viola *et al.* 2015).

Most data in this field are retrospective and are not totally convincing, because the risk of recurrence and of cancer-related death is low and benefits expected from any intervention might therefore be only marginal. Prospective randomized controlled trials are needed in low-risk patients to validate the use of hemithyroidectomy vs total thyroidectomy and the absence of benefits of prophylactic central neck dissection; a randomized trial on the latter issue is ongoing (ESTIMABL3 trial, NCT03570021).

Post-operative administration of RAI

The first administered activity of RAI after total thyroidectomy has three main goals: (1) to destroy presumably benign residual thyroid tissue (ablation) that improves the sensitivity of serum Tg measurement during follow-up, (2) to destroy suspected but not identified remaining disease (adjuvant treatment) or known persistent or recurrent disease (treatment) that may improve the disease free survival (DFS) and overall survival (OS), (3) to perform a highly sensitive post-treatment whole-body scan (WBS) a few days after RAI

administration that provides whole-body disease staging. The role of routine RAI administration is controversial in these low-risk patients who have a 1–3% risk of persistent disease after surgery. Several retrospective studies have not found any benefit for RAI treatment in terms of DFS or OS in low-risk patients (Lamartina *et al.* 2015). On the other hand, the rare patients with evidence of structural residual disease after surgery are candidates for a high activity (3.7 GBq) RAI treatment (Berdelou *et al.* 2018).

Pre-ablation, post-operative Tg and neck US predict the results of the post-treatment WBS and are useful in deciding whether or not to perform RAI remnant ablation. In fact, when post-operative serum Tg is either <1 ng/mL following rhTSH stimulation or Tg <0.2 ng/mL on levothyroxine treatment (in the absence of detectable Tg antibodies), and the neck US is normal, patients are already in ‘excellent response’ (Table 2) and serum Tg can be reliably used for the subsequent follow-up. In this setting, uptake of RAI outside the thyroid bed is rare and RAI administration is not indicated (Matrone *et al.* 2017, Schlumberger *et al.* 2018). When serum Tg is detectable (either on levothyroxine treatment or following rhTSH stimulation), the risk of persistent disease increases with the serum Tg level. In this setting, the indication for the administration of RAI should take into account the level of serum Tg and the other prognostic indicators. If the serum Tg level is detectable but low, these patients might be followed up with RAI administration only in case of increasing Tg levels, with the aim of destroying normal thyroid remnants and eventually treating occult persistent disease. There is no evidence in these low-risk patients that delayed administration of RAI decreases the chances for cure. These data are expected to be confirmed by two ongoing randomized prospective trials (ESTIMABL2 trial number: NCT01837745 and IoN trial number: NCT01398085) comparing the outcome of ablation with rhTSH and 1.1 GBq versus no RAI in low-risk patients.

Two prospective randomized trials have shown that the ablation rate was not inferior with rhTSH stimulation versus prolonged thyroid hormone withdrawal or with a low (1.1 GBq) activity versus a high (3.7 GBq) activity (Mallick *et al.* 2012, Schlumberger *et al.* 2012). Therefore, in the few low-risk patients without persistent structural disease who are candidates for RAI ablation, a low RAI activity (1.1 GBq) following rhTSH administration should be used. Recent reports have shown that after a 5-year follow-up, this protocol is not associated with an increased need of further treatments (surgery or RAI) nor with an increased risk of persistent or recurrent disease (Schlumberger *et al.* 2018, Dehbi *et al.* 2019).

Iodine metabolism is impaired in *BRAFV600E*-mutated tumors (Durante *et al.* 2007). Whether and in which *V600EBRAF*-mutated tumors should RAI be administered post-operatively is controversial because RAI might be less efficient in these tumors.

Follow-up

Most low-risk DTC patients have no evidence of disease after initial treatment (excellent response), and recurrence is highly unlikely to occur in these cases (Vaisman *et al.* 2011). Therefore, they do not need aggressive follow-up. The cost of the detection of a recurrence is 6–7 times higher in patients with a low-risk DTC than in patients with an intermediate-risk or high-risk DTC, due to the lower prevalence of recurrence (Wang *et al.* 2015). Identifying a cost-effective follow-up strategy for this large subset of patients is therefore a priority.

Serum thyroglobulin

Serum Tg is a sensitive marker for the presence of thyroid tissue. Tg can be produced by both normal and neoplastic thyrocytes, and the thresholds used to define responses to treatment (Table 2) differ depending on whether residual normal thyroid tissue is present following primary treatment (that is, in patients treated with total thyroidectomy without RAI remnant ablation or those who underwent hemithyroidectomy). Such thresholds still need to be validated for clinical practice.

Given the lack of standardization between assays, Tg should be measured using the same method either with a functional sensitivity of ~1 ng/mL (‘classic’ assays) or preferably with a functional sensitivity ~0.1–0.2 ng/mL (ultrasensitive assays) (Schlumberger *et al.* 2007). The sensitivity of classic serum Tg assays for tumor detection can be increased by TSH stimulation obtained either with prolonged levothyroxine withdrawal or injections of recombinant human TSH in patients treated with both total thyroidectomy and RAI ablation. The negative predictive value of undetectable Tg after TSH stimulation in these patients is close to 100% (Pacini *et al.* 2001b, Torlontano *et al.* 2006, Castagna *et al.* 2008, Crocetti *et al.* 2008). Therefore, if the initial TSH-stimulated Tg measurement reveals an undetectable level, further TSH-stimulated Tg testing offers no benefit and is not recommended (Haugen *et al.* 2016).

The availability of ultrasensitive Tg assays seems to obviate the need for routine TSH-stimulated Tg

determinations. TSH stimulation produces a 5- to 10-fold increase over basal values in serum Tg levels, and thus using an ultrasensitive assay which is ten times more sensitive than classic assays, comparable sensitivity for tumor detection is provided with the basal serum Tg measurement without any TSH stimulation. The cutoff for the best accuracy for basal ultrasensitive Tg has been reported as 0.2–0.3 ng/mL (Schlumberger *et al.* 2007).

TSH-stimulated Tg determination may be informative in patients with low basal serum Tg level (<1 ng/mL) who are classified as 'indeterminate response' (see below): a low stimulated Tg level is reassuring, but a higher level (>2 ng/mL) is suspicious for persistent disease and indicates a more compulsive follow-up (Brassard *et al.* 2011).

TSH stimulation obtained either with prolonged levothyroxine withdrawal or injections of recombinant human TSH increases the production of Tg in the serum by both normal residual thyroid tissue and neoplastic tissue. Therefore, there is no role for TSH stimulation in patients treated with surgery alone, without RAI ablation. These patients should be followed up with unstimulated serum Tg measured while on levothyroxine treatment, and the trend over time of serum Tg should be interpreted by taking into account the serum TSH level.

Anti-thyroglobulin antibodies

In the presence of TgAb, the results of serum Tg assays cannot be reliably interpreted: depending on the specific assay used, false-negative or (less frequently) false-positive results will emerge (Spencer & Fatemi 2013). As a consequence, the presence of TgAb should always be assessed at the time of serum Tg measurements (Haugen *et al.* 2016). This problem has been overcome in experimental settings with mass spectrometry assays, but this approach seems to be less effective in clinical practice (Netzel *et al.* 2015, Azmat *et al.* 2017). Monitoring TgAb titers over time (using the same assay) can provide surrogate information on disease recurrence, and declining titers are usually associated with remission (Matrone *et al.* 2018). An important variability exists between commercially available TgAb assays, and as a consequence the same assay should be used to monitor TgAb titers over time (Latrofa *et al.* 2012).

The presence of heterophilic antibodies that are not detected by commercial TgAb assays may result in false-positive Tg measurements. These false-positive results are suspected when serum Tg that is detectable on levothyroxine treatment does not increase following TSH stimulation. The use of heterophile-blocking tubes

can overcome this problem (Preissner *et al.* 2003, Massart *et al.* 2008).

Neck ultrasound and cytology

Most recurrences of PTCs are found in the neck and can be detected by ultrasound (Durante *et al.* 2013b). The documented increased use of neck-US in DTC patients observed between 1998 and 2011 was associated with increased rates of treatment (surgery or RAI), but not with improved survival rates (Banerjee *et al.* 2016).

The European Thyroid Association guidelines identify groups of ultrasonographic characteristics that can be used to distinguish normal (benign), indeterminate and suspicious findings (Table 3) (Leenhardt *et al.* 2013). However, up to 18% of histologically benign lymph nodes have suspicious features on ultrasonography (Leboulleux *et al.* 2007a).

Roughly two-thirds of neck lymph nodes classified as indeterminate on ultrasound will spontaneously disappear after several months, so watchful waiting is appropriate for small indeterminate nodes. Overall, only a small proportion of these lymph nodes will grow over time, but no complication due to size increase has been reported during follow-up (Rondeau *et al.* 2011, Robenshtok *et al.* 2012, Lamartina *et al.* 2016b).

Recurrences in the surgical bed usually appear hypoechoic with microcalcifications, cystic components, irregular margins, and increased vascularity, but false-positive ultrasonographic findings are frequent (26–35%) in particular during the early follow-up period due to the presence of inflammation and scar tissue (Lamartina *et al.* 2016a).

Fine-needle aspiration cytology (with Tg assay in the washout fluid) is recommended only if the cytology results will potentially change management decision. It is indicated for suspicious nodes in potentially threatening locations, or that persist and grow over time, or central or lateral nodes whose short axis measures more than 8 or 10 mm, respectively (Grani & Fumarola 2014, Haugen *et al.* 2016). Small non-threatening lesions can be managed with repeat neck-US examinations every 6–12 months (Haugen *et al.* 2016). US follow-up cannot be withdrawn in these patients, and fine-needle aspiration cytology may be considered after some years of follow-up in order to avoid the follow-up of false-positive US findings.

The role of neck US in the follow-up of FTC and HCC is limited given the higher risk of distant metastases (up to 85% of the cases) and rarer thyroid bed or lymph node recurrence (Grani *et al.* 2018).

Table 3 Ultrasound features suspicious for malignancy of neck lymph nodes.

Sign	Sensitivity, %	Specificity, %	NPV, %	PPV, %	Accuracy, %	% of normal LN with the sign
Suspicious neck lymph nodes: any of the following: microcalcifications, cystic component, peripheral or diffusely increased vascularization, parenchymal hyperechoic tissue looking like thyroid tissue						
Microcalcifications	5–69	93–100	33–60	88–100	56–72	0
Cystic component	10–34	91–100	30–66	77–100	48–65	0
Peripheral vascularization	40–86	57–93	31–70	77–80	54–71	1–18
Hyperechogenicity (thyroid tissue like)	30–87	43–95	38–84	66–96	56–90	4–17
Indeterminate neck lymph nodes: hilum not evident and at least one of the following criteria: round shape, increased short axis (≥ 8 mm in level II and ≥ 5 mm in levels III and IV), increased central vascularization						
Round shape	37	70	45	63	–	4–36
Hilum absent	100	29	–	–	–	–
Normal neck lymph nodes: Hilum present, ovoid shape and normal size, absent or hilar vascularization. Absence of suspicious signs						
Hilum present	0–0.5	–	–	–	–	29–48
Absent vascularization	0	–	–	–	–	33–36

Whole-body radioactive iodine scan

Before the introduction of neck-US in clinical practice, diagnostic RAI WBS was the cornerstone of the follow-up of DTC. These scans were performed to assess the completeness of ablation at 6–18 months after RAI ablation, but successful ablation is now defined as the association of undetectable serum Tg (in the absence of Tg antibodies) and normal neck-US. Several retrospective studies have shown that diagnostic WBS are less sensitive in detecting recurrence than a combination of serum Tg and neck-US (Pacini *et al.* 2001a, Torlontano *et al.* 2006). Therefore, in the absence of RAI uptake outside of the thyroid bed on the first WBS after RAI administration there is no need for repeated diagnostic WBS during follow-up (Cailleux *et al.* 2000, Pacini *et al.* 2002).

Cross-sectional imaging

Given the rarity of distant metastases in patients with low-risk DTC, cross-sectional imaging including computed tomography scan, MRI and 18 fluorodeoxyglucose positron emission tomography (18-FDG-PET) are not routinely used in these patients, but can provide valuable information in certain cases (Leboulleux *et al.* 2007b, Lamartina *et al.* 2016a, Grani *et al.* 2018).

Follow-up strategies

In 1994, recurrences of PTC were observed up to 40 years after diagnosis (Mazzaferri & Jhiang 1994). In a more recent cohort, nearly 80% of recurrences were identified

within 5 years of diagnosis (Durante *et al.* 2013b). The difference between these two data sets reflects the enhanced sensitivity of contemporary diagnostic tools employed for follow-up of PTC. This increased sensitivity leads to the earlier discovery of persistent or recurrent tumor foci, but it is not clear whether and to what extent this early diagnosis actually improves patient outcomes. Furthermore, the increased sensitivity of diagnostic tools can also increase the frequency of false-positive results (Peiling Yang *et al.* 2015).

Excellent response to total thyroidectomy and radioactive iodine ablation

The response to total thyroidectomy and RAI remnant ablation is assessed with serum Tg (either basal or TSH-stimulated) and neck-US (Table 2) (Haugen *et al.* 2016). For patients with low-risk PTC at initial treatment, an excellent response to treatment is associated with a subsequent recurrence rate of <1% (Haugen *et al.* 2016).

In rare cases, serum Tg may fail to identify small foci of disease, usually in the neck, which can be detected with neck-US (Torlontano *et al.* 2004). However, neck-US often identifies nonspecific findings that are much more frequent than true tumor recurrences (false positives) and that may lead to unnecessary procedures. In retrospective cohorts of patients with a low-risk of recurrence, the rate of false-positive neck-US findings varied from 8.3 to 67% (Peiling Yang *et al.* 2015, Lamartina *et al.* 2016b), whereas after a median follow-up of 8 years, structural tumor recurrence was confirmed in 1% of cases (Durante *et al.* 2013b). In a prospective study of 631 low-risk patients with an excellent response to treatment, only one neck

recurrence was observed on neck-US with a median follow-up of 5 years (Schlumberger *et al.* 2018). In another prospective study of 226 intermediate- and low-risk PTC patients with an excellent or indeterminate response to treatment at 1 year, only one patient had a suspicious neck-US with an increased titer of TgAb that did not require any further treatment, and seven patients had indeterminate neck-US findings (Grani *et al.* 2019). The benefits of early diagnosis on patient outcomes have not been demonstrated, and the ATA guidelines recommend simple surveillance for small suspicious lymph nodes. Consequently, in the absence of any other abnormalities at the first-year assessment, subsequent neck-US can be deferred until serum Tg becomes detectable (>0.2 ng/mL).

Levothyroxine treatment should be titrated to obtain a normal-low TSH level (0.5 – 2 μ UI/mL) (Haugen *et al.* 2016). Suppression of TSH is not expected to provide any benefit in this setting (Sugitani & Fujimoto 2010, Lamartina *et al.* 2018b), and it might cause several side effects, including cardiac arrhythmia, osteoporosis, and symptoms of anxiety/insomnia (Biondi & Cooper 2010, Sugitani & Fujimoto 2011).

The follow-up can be limited to periodic (12–24 months) measurements of TSH, serum Tg and TgAb while on levothyroxine treatment. There is no need to perform these routine assessments in a specialized center after the first 5 years of follow-up, the risk of recurrence is negligible thereafter and periodic (12–24 months) TSH, serum Tg and TgAb levels on levothyroxine treatment assessments can be assured by the general practitioner.

Biochemical incomplete response to total thyroidectomy and radioactive iodine ablation

Six to 18 months after primary treatment, detectable serum Tg in the absence of structural disease on imaging studies (Table 2) is found in approximately 10% of patients with low-risk PTC (Tuttle *et al.* 2010). This biochemical incomplete response is generally monitored every 6–12 months with serum Tg and TgAb assessments. Stable or declining serum Tg levels over time are associated with disease remission, and criteria for an excellent response will be observed in up to two-thirds of these patients without any additional treatment (Baudin *et al.* 2003, Vaisman *et al.* 2012, Lamartina *et al.* 2016c). In contrast, rising serum Tg levels over time are suspicious for persistent disease and should be explored with neck-US and other imaging modalities, if needed. A whole-body imaging technique (18-FDG-PET or cross-sectional imaging) should be considered for FTC and HCC patients

and for those with aggressive histotypes given the high risk of distant metastases (Grani *et al.* 2018).

Rapid (<12 months) Tg doubling time is associated with a worse outcome (Miyauchi *et al.* 2011). Also, rising TgAb titers have been associated with an increased risk of recurrence, as compared with stable or declining TgAb titers (Rosario *et al.* 2016, Ernaga-Lorea *et al.* 2018).

Indeterminate response to total thyroidectomy and radioactive iodine ablation

In the presence of nonspecific abnormalities on imaging studies or low detectable serum markers (Tg or TgAb; Table 2), the treatment response is classified as indeterminate. An indeterminate response is observed in 12–23% of low-risk patients, but 80–90% of these patients will never experience structural disease recurrence (Tuttle *et al.* 2010).

a) Low detectable serum markers

The clinical relevance of low but detectable basal levels of Tg is unclear. An analysis of TSH-stimulated serum Tg may be helpful in these cases. In patients with a minimal increase in TSH-stimulated Tg (<2 ng/mL), serum levels of Tg will probably normalize spontaneously with time. In patients with larger increases in stimulated serum Tg (>2 ng/mL), the likelihood of persistent disease increases with the level of stimulated Tg (Brassard *et al.* 2011). If stimulated Tg testing is repeated 5 years after the initial treatment, the vast majority of responses originally classified as indeterminate (up to 98%) can be re-classified as excellent (Lamartina *et al.* 2016c). Again, in this setting the trend of serum Tg and TgAb over time should be taken into consideration to establish the pace of assessments (usually performed on a yearly basis) and the indication for imaging other than neck-US (Hartl *et al.* 2019).

b) Nonspecific abnormalities on imaging studies

Indeterminate neck-US findings are defined in Table 3. As discussed in the former sections, false-positive findings are far more common than true relapses in low-risk patients. Most indeterminate findings will spontaneously disappear during follow-up. In a series of 403 PTC patients with indeterminate response to treatment, none of the 161 patients with indeterminate findings on neck-US or faint uptake in thyroid bed on diagnostic WBS with undetectable Tg and TgAbs experienced tumor recurrence (Oh *et al.* 2019). In case of persistent, growing, threatening lesions, fine-needle

aspiration cytology (and needle washout Tg testing) should be considered to prove recurrence.

Structural incomplete response to treatment

Strategies for the management of structural disease should take into account the disease burden, its location (or locations) and the pace of disease progression. The most common site of persistent or recurrent PTC is the neck. These lesions are classified according to their ultrasonographic characteristics. Fine-needle aspiration cytology (with measurement of Tg in the washout fluid) is advisable for suspicious lesions when a positive result can be expected to alter the management plan (Haugen *et al.* 2016). Treatment of neck recurrences may include RAI, surgery (Lamartina *et al.* 2017a) or focal treatment modalities such as ethanol injection (Heilo *et al.* 2011, Hay *et al.* 2013).

18-FDG-PET can be a useful diagnostic tool for whole-body examination, including bones, and seems to be the most sensitive tool for imaging patients with elevated serum Tg levels (Leboulleux *et al.* 2007b, Leboulleux *et al.* 2012). It should be performed as the first-line imaging modality. It can also provide prognostic information (Robbins *et al.* 2006).

Diagnostic WBS is rarely indicated but it may be used to avoid the administration of a higher therapeutic activity in patients with structural disease demonstrated on cross-sectional imaging with no detectable RAI uptake. In such cases, even if uptake is present on post-therapeutic WBS, it might be too low to deliver an efficient radiation dose to tumor foci (Sabra *et al.* 2012).

Levothyroxine suppressive treatment was associated with reduced recurrence rate and cancer-related mortality in high-risk patients (Jonklaas *et al.* 2006). Even if the optimal TSH level is still unclear in patients with structural disease, suppression to undetectable TSH levels does not seem to provide further benefit compared with mild suppression for these patients (Carhill *et al.* 2015), and the level of suppression should be weighed against the risk of side effects (Haugen *et al.* 2016).

Total thyroidectomy without ablation

The 2015 ATA guidelines restricted the indication for RAI remnant ablation to selected low-risk DTC patients. As a result, clinicians will be faced more frequently with patients with some amount of residual normal thyroid tissue that produces detectable Tg levels in the serum. The volume of such residual tissue will depend on the extent

of thyroid surgery (hemithyroidectomy versus total thyroidectomy) and the skill of the surgeon. Neck-US is informative even in the presence of residual thyroid tissue, however.

The serum Tg levels proposed for defining responses to treatment in patients who underwent total thyroidectomy without RAI remnant ablation are reported in Table 2 (Momesso *et al.* 2016). In centers with 'high-volume' surgeons (defined as surgeons who perform at least 40 surgical procedures for thyroid cancer/year), up to 60% of patients treated with total thyroidectomy have undetectable Tg levels (<0.2 ng/mL) at the first assessment on levothyroxine treatment, and the percentage rises to 75% or more after 5 years (Durante *et al.* 2012, Nascimento *et al.* 2013). These figures might be different for patients treated by low-volume surgeons because larger amounts of residual tissue might persist rendering Tg interpretation more challenging. In patients with detectable serum Tg and without any other evidence of disease, the Tg level is usually low (usually <1 ng/mL) and its trend over time on levothyroxine treatment will allow clinicians to identify the few patients with rising levels of Tg or TgAb that may harbor persistent or recurrent disease and for whom the option of imaging modalities and of an empiric administration of a high RAI activity should be considered.

Levothyroxine treatment should be titrated to maintain TSH level in the low normal range (0.5–2 µUI/mL) (Haugen *et al.* 2016).

In summary, periodic (once every 6–12 months) evaluation on levothyroxine treatment with serum levels of unstimulated Tg and TgAb determinations is performed in these patients. Neck-US is performed in patients with an increasing trend of serum Tg or TgAb over time (Grani *et al.* 2019). The evidence supporting the proposed cutoffs and follow-up strategies relies on retrospective studies and further evidence is needed for validation.

Patients treated with hemithyroidectomy

Hemithyroidectomy is an option for patients with low-risk, intrathyroidal PTCs that are less than 4 cm in diameter (T1-T2 tumors) and with a normal contralateral lobe at pre-operative neck-US (Haugen *et al.* 2016). The risk of tumor recurrence is by definition low, but may occur in neck lymph nodes and/or contralateral lobe. The appearance during follow-up of benign nodules (which occurs in 20–50% of patients) is far more common than the appearance of cancer recurrence, which is seen in about 5% of patients who undergo hemithyroidectomy

(Matsuzo *et al.* 2014). A consistent proportion of these recurrences will probably remain microscopic and have no clinical significance.

Serum Tg is usually detectable in these patients and its serum level is higher in patients who do not receive levothyroxine treatment. Its sensitivity for the detection of persistent and recurrent disease is lower than that in patients with small amount of normal thyroid tissue and an increasing trend over time should indicate a neck-US.

Up to two-thirds of patients treated with hemithyroidectomy will remain euthyroid with a serum TSH level within the normal range (Johner *et al.* 2011). Levothyroxine treatment aimed at keeping TSH in normal-low range might be considered but is not mandatory in these cases. Whether levothyroxine treatment might prevent the development of benign nodules is still controversial. Good quality evidence demonstrates that TSH suppression is not effective in preventing cancer recurrence in low-risk PTC patients (Sugitani & Fujimoto 2010, Park *et al.* 2017) and may have non-negligible side effects (Biondi & Cooper 2010, Sugitani & Fujimoto 2011).

Conclusion

In most low-risk patients, initial treatment includes surgery (total thyroidectomy or hemithyroidectomy without prophylactic lymph node dissection) and selective use of post-operative RAI. This strategy does not increase the risk of recurrence or of cancer mortality and still permits a reliable follow-up.

Several follow-up tools are available for DTC patients, but in most low-risk cases, a very simple assessment schedule is sufficient. This may include a yearly determination of serum TSH, Tg and TgAb for 5 years and then every 2 years, with neck ultrasound being performed only in patients with abnormal biochemical or clinical findings. Long-term follow-up does not need a referral to a specialized center.

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