Follow-up of low risk thyroid cancer patients: can we stop follow-up after 5 years of complete remission?

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Abstract

Each year, the proportion of thyroid cancer patients presenting with low-risk disease is increasing. The shift in the landscape of thyroid cancer presentation is forcing clinicians to re-evaluate not only management but also surveillance paradigms. During the follow-up, patients are stratified considering their response to treatment and classified into one of the following response categories: excellent, biochemical incomplete, structural incomplete, or indeterminate. These categories reflect a real-time prognosis and thereby substantially influence and personalise disease management. Although at present, no guideline recommends stopping differentiated thyroid carcinoma (DTC) surveillance at any particular time point, the relatively low prevalence of treatment failures in low-risk patients may prompt early discontinuation of surveillance in this subgroup. Therefore, this debate will present an overview of the controversies surrounding the surveillance of low-risk patients with DTC.

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Introduction

Thyroid cancer incidence is rising considerably worldwide (+300% over the last 30 years) (1, 2). The causes underpinning this huge increase are controversial and environmental factors may play a role (1) as well as an overdiagnosis effect due to the widespread use of imaging techniques and screening campaigns (3).

In order to limit this phenomenon, the US Preventive Services Task Force recommends against thyroid screening in the general population (4). This statement does not apply to subjects with recognized risk factors of thyroid cancer (i.e. subjects exposed to ionizing radiation in childhood and kindreds with familial non-medullary thyroid cancer) for whom a 'low intensity' screening by means of thyroid palpation may be considered (5).

The vast majority of newly diagnosed differentiated thyroid cancers (DTC) are small, intrathyroidal papillary tumors (2, 6). In order to assist clinicians in the

management of this growing number of DTC patients, several risk stratification tools are available.

The American Joint Committee on Cancer (AJCC) and Union International Contre le Cancer (UICC) Tumor Node Metastasis (TNM) staging system is a tumor classification aimed at mortality prediction. Overall, the risk of thyroid cancer death is low (less than 2% at 5 years) (<https://seer.cancer.gov/statfacts/html/thyro.html> last accessed November 21st, 2019) and less than 2% of DTC have a substantial mortality risk (i.e. stage III and IV) according to AJCC/UICC TNM staging 8th edition (7, 8).

Nonetheless, DTC patients can experience disease persistence or recurrence in up to 50% of the cases (9).

The risk of recurrence classification proposed by the 2015 American Thyroid Association (ATA) guidelines is based on clinical and pathological features available at the

moment of primary treatment (surgery with or without radioiodine).

According to this classification, low-risk DTC are intrathyroidal tumors with no local or distant metastatic spread and no aggressive histological features, including vascular invasion in papillary thyroid cancer and less than four vascular invasion foci in minimally invasive follicular thyroid cancer (9). Tumors with less than five microscopic (<2 mm) metastatic lymph nodes should be considered also as low risk (9). Overall, the estimated recurrence risk is $\leq 5\%$ (9).

Minimal extrathyroidal extension is a part of intermediate risk features according to 2015 ATA guidelines, but it is not anymore taken into account in AJCC/UICC TNM classification 8th edition, due to its limited role in thyroid cancer death prediction (8).

The initial risk estimate can be refined with the information obtained after 6–18 months of follow-up. Such disease assessment is based on serum thyroglobulin (Tg) and anti-thyroglobulin antibodies (TgAb) assessment and imaging, usually neck ultrasound (neck-US) (9). When an excellent response to treatment is achieved (i.e. undetectable Tg without TgAb, no abnormal findings on imaging), the risk of recurrence of patients initially classified as at intermediate risk drops from 35–40% to 1–2% (10, 11). According to the ATA guidelines, excellent response should lead to decrease the intensity and the frequency of follow-up.

High-risk patients are on the opposite end of the DTC spectrum of aggressiveness. In this group, even excellent response confers a 14% risk of recurrence (12) and late tumor recurrence are observed up to 35 years after diagnosis (13). As a consequence, lifelong follow-up has been recommended for DTC patients.

Although, at present, no guideline recommends stopping DTC surveillance at any time point, contemporary DTC panorama has radically changed questioning lifelong surveillance.

This debate article will overview the controversies surrounding the surveillance of low-risk DTC patients according to the response to primary treatment and the challenges posed by the evolution of therapeutic strategies.

'Follow-up of low-risk thyroid cancer patients: can we stop follow-up after 5 years of complete remission?' Pros

Low risk tumors represent the majority of DTC

Contemporary longitudinal cohorts of DTC patients consist of low-risk tumors by roughly two-thirds (14).

The evolution of risk classifications and pathologic classifications over time plays a role in accentuating these numbers. The risk of recurrence classification proposed by the 2015 ATA guidelines lists in the low-risk category patients with less than five lymph nodes with microscopic metastatic foci (<2 mm) (9). This change led to the downstaging of about 25% (7) of these patients that were previously considered as intermediate risk according to 2009 ATA guidelines (15). With regard to survival prognostic tools, the proportion of DTC classified as low stage is increased by about 30% with the implementation of the 8th edition of AJCC/UICC TNM (7). Moreover, a new nosologic entity was introduced with the 2017 WHO classification of tumors: the 'noninvasive follicular thyroid neoplasm with papillary-like nuclear features' (NIFTP) (16). NIFTP was previously considered within the follicular variant of papillary thyroid cancer and is associated with an excellent prognosis with anecdotal cases of neck lymph node metastasis and recurrence (<1%) (17). NIFTP is not considered a cancer, and its introduction in thyroid tumor classification has led to refine the cancer risk estimates of current cytologic classifications (the risk of malignancy is decreased by 14% and 3% in the Bethesda V and VI category respectively) (18). NIFTPs were initially estimated to represent nearly 20% of all PTCs (16). Further epidemiological studies reported percentages ranging from 16% (19) to about 1% (20). For these patients, no TNM classification is recommended (the risk of thyroid cancer death is virtually zero) and according to ATA 'occasional monitoring with serum thyroglobulin and neck ultrasound can be considered, depending upon patient context, but this is not mandatory' (21). These recommendations are based on weak evidence due to the scant experience with this new entity available to date, and further evidence is needed to validate these recommendations.

Another category of patients with excellent prognosis are intrathyroidal and have unifocal PTC of 10 mm or less, with no local or distant metastases, no aggressive histologic variant, and no history of familial non-medullary thyroid cancer or head and neck radiotherapy in childhood (so called very low-risk PTC) (22). These tumors have an excellent prognosis with or without radioiodine treatment and when excellent response is achieved the risk of recurrence is virtually zero (22). These very low-risk PTC represent about two out of three of all PTC of 10 mm or less (the so called microPTCs) and a considerable percentage of all DTCs (about 23%) (14).

The costs of surveillance of this growing number of low-risk DTC are important. With regard to the healthcare system, it has been estimated that the cost of

one recurrence diagnosis in low risk was six and seven times greater than in intermediate and high-risk patients, respectively (23). Moreover, a hidden social cost in terms of patient anxiety and depression is emerging in thyroid cancer patients despite a good prognosis (24) and thyroid cancer is recognized as a cause of patient financial bankruptcy (25).

In this context, the issue of effective management of low-risk DTC and a possible end of life-long surveillance is a priority.

Unlikely DTC cohorts diagnosed and followed-up between the 50s and early 90s, in which late recurrences were described up to 35 years after diagnosis (13, 26), in contemporary cohorts the rare patients with recurrence are found in nearly 80% of the cases within 5 years from primary treatment (27, 28, 29, 30). The stage of disease at the moment of diagnosis changed over time too, with a significant trend toward an early-stage presentation (31).

The availability of very sensitive diagnostic tools has played a crucial role in this shift in DTC panorama. Increased use of imaging (e.g. Doppler examination of carotid arteries), as well as screening campaigns, led to frequent diagnosis of small, early-stage DTC (3, 32, 33). (This phenomenon was not mirrored by an improvement in DTC survival.) The use of different thyroid nodule size cutoffs for fine-needle aspiration biopsy indication based on the risk estimated by ultrasonographic scoring systems (34) may help to limit the phenomenon of overdiagnosis (35).

With regard to DTC follow-up, imaging assessments used to be performed with radioiodine diagnostic whole body scan (DxWBS) that has excellent specificity (100%) but a very low sensitivity (34%) in neck recurrence identification (36). NeckUS and serum Tg testing available nowadays are far more accurate tools compared with DxWBS for the detection of neck recurrence (36, 37, 38, 39, 40, 41).

The absence of abnormal findings on neck US coupled with TSH-stimulated serum Tg <1 ng/mL, in the absence of TgAbs, has a negative predictive value approaching 100% (42, 43).

After a first TSH-stimulated Tg result <1 ng/mL, there is no benefit of further TSH-stimulated Tg testing (44, 45, 46). The diagnostic performance of undetectable serum Tg measured with an ultrasensitive assay on levothyroxine treatment is comparable to that of TSH-stimulated Tg (29, 47, 48). As a consequence, the definition of excellent response (i.e. complete remission) can be based either on stimulated Tg <1 ng/mL or ultrasensitive Tg on levothyroxine treatment <0.2 ng/mL (9) associated to no abnormal imaging findings (9).

Excellent response is achieved in 80–90% of low-risk patients at the 6–18 months assessment (10, 11, 49).

Combining the initial risk estimates to the results of the 6–18 months assessment (ongoing risk assessment) allows better estimates of patients' outcomes (10, 11, 49). The risk of recurrence becomes extremely low (less than 2%) after the achievement of an excellent response in both low and intermediate risk DTC patients (10, 11, 49).

It is worth noting that these risk estimates in large part stem from retrospective studies, some with relatively short follow-up periods. Several risk stratification tools (e.g. AGES, GAMES, TNM) have been employed, rendering the comparison between the different study populations difficult. Indeed, some 'low risk' populations include a consistent proportion of patients with lymph node metastases (without mention on the number and size of the metastatic nodes) that could fall in the intermediate or high risk categories according to the ATA classification or patients with gross extrathyroidal extension that fall into the high risk category (50).

Considering DTC patients that fulfill the ATA low-risk definition, recurrence rates range between less than 1% and 2% in large retrospective cohorts with long follow-up periods (10–15 years) (51, 52).

The presence of specific somatic tumor mutations has been integrated into the ATA risk stratification classification (9). Although the presence of BRAFV600E mutation has been associated with higher recurrence rates in tumors of >1 cm (53) that are considered as at intermediate risk of recurrence, this is not true for intrathyroidal microPTCs (54).

Diagnostic tools limitations and gray zone responses

TgAbs are found in about 20% of DTC patients (55). False-negative and, less frequently false-positive, Tg results can occur in the presence of TgAbs using common laboratory immunometric or radioimmunometric assays (55). The use of mass spectrometry may overcome this limitation, but the results obtained in real-life clinical practice are less convincing (56) than those obtained in an experimental setting (57, 58). A stable or declining trend of serum TgAbs over time is associated with disease remission (59, 60), nonetheless these patients cannot be classified as excellent response until TgAb become negative (9).

The positive predictive value of Tg is poor. Persistence of detectable serum Tg in the absence of suspicious findings on imaging is found in about 20% of low-risk DTCs (10, 11, 49). This situation is called biochemical-

incomplete response (≥ 1 ng/mL for Tg on levothyroxine treatment and above 10 ng/mL for stimulated Tg) or indeterminate response to treatment (low detectable serum Tg between >0.2 ng/mL and <1 ng/mL for Tg on levothyroxine treatment and between >1 ng/mL and <10 ng/mL for stimulated Tg) (9).

Patients with rising levels of TgAbs over time in the absence of suspicious findings are considered as biochemical-incomplete response and the presence of stable or declining titers of TgAbs in the absence of suspicious findings on imaging is considered as an indeterminate response to treatment (9).

Only $\leq 36\%$ and $\leq 11\%$ of low-risk DTC patients with biochemical-incomplete and indeterminate response will develop structural disease, respectively (10, 11), and Tg will spontaneously decrease to undetectable values fulfilling the definition of excellent response in a percentage between 50 and 80% of these patients.

Repeating stimulated Tg testing in these patients at the fifth year of follow-up after primary treatment can help to reclassify these patients as in excellent response (in up to 98% of patients initially classified as indeterminate response and in 40% of the patients classified as a biochemical-incomplete response) (61).

Also, neck-US can lead to false-positive results in low-risk patients that are more frequent (8–67%) than true recurrences (1–1.2%) (62, 63, 64). The classification of neck-US findings as indeterminate or suspicious according to the classification proposed by the European Thyroid Association (41) and endorsed by the ATA (9) can help to identify the lesions that harbor suspicious features and deserve further attention (38). About two-thirds of neck lymph nodes classified as indeterminate will spontaneously disappear (38). Simple surveillance is a safe approach for the management of these indeterminate lesions (38, 65, 66).

Fine-needle cytology coupled with Tg assay in needle washout fluid (67) is effective in recurrence identification, but it is indicated only if the results will change the management of the patients (9). Fine-needle cytology and Tg washout can be considered in small indeterminate lesions stable over several years to avoid the risk of long-term ultrasonographic follow-up of benign lesions (68).

Another pitfall of neck-US is follicular and Hürthle cell thyroid cancer follow-up: both these rarer variants of DTC disclose more frequently distant metastases and less frequently neck lymph node recurrence compared with PTCs (69), and whole body imaging should be considered in case of biomarkers abnormality, namely in the biochemical-incomplete response range (70). An

important prognostic factor is the presence and the extent of vascular invasion. The 2017 World Health Organization classification proposed to separate these tumors into three subtypes: presence of capsular invasion without vascular invasion (true minimally invasive tumor), presence of limited vascular invasion, and extensive invasion of vessels and surrounding tissues (widely invasive tumor) (71). Only true minimally invasive tumors should be considered as low risk (69, 70). More evidence is needed to characterize the optimal management of these tumors.

Treatment paradigm shift

As a consequence of the increased awareness of the excellent prognosis of DTC, in the last years, the traditional one-size-fits-all therapeutic approach of DTC, consisting of total thyroidectomy and radioiodine treatment, was progressively replaced by an attempt to a risk guided management.

The mainstay of thyroid cancer treatment is surgery. Nonetheless, a growing body of evidence is demonstrating that active surveillance is a safe option in very low-risk microPTCs (72), notably in older patients (73, 74). An accurate selection of candidates for active surveillance is mandatory, the preference of the patient for this option is essential as well as the availability of a regular ultrasonographic follow-up in a referral center (75).

In low-risk intrathyroidal DTC of ≤ 40 mm in size the preferred surgical treatment should be hemithyroidectomy (9). The rate of surgery-related complications is lower with hemithyroidectomy compared with total thyroidectomy (76), even in experienced hands (77), and levothyroxine replacement treatment can be avoided in a considerable percentage of the patients (between a half and two-thirds) (78, 79, 80).

No difference in terms of overall survival was observed comparing patients treated with total thyroidectomy with those treated with hemithyroidectomy after adjusting patients and clinical characteristics in a large DTC cohort (81, 82, 83).

The rates of recurrence are low in patients treated with hemithyroidectomy: recurrence in the contralateral lobe was observed in about 5% of the cases (83, 84, 85, 86) and lymph node recurrence in a percentage ranging between less than 1% and about 3% (83, 85, 86). No cases of distant recurrence are described when only a low-risk population is taken into account (83, 85, 86). Retrospective cohorts have found no significative difference in terms of neck recurrence (lymph nodes and thyroid bed), comparing patients treated with hemithyroidectomy with those

treated with total thyroidectomy (83). The mean time interval from initial treatment and recurrence was 4 years in a study of 734 patients treated with hemithyroidectomy (85), but late recurrences are possible (84).

The other cornerstone of DTC treatment is radioiodine treatment (RAI-T). The goals of RAI-T are: (1.) to improve survival treating metastatic disease, (2.) to reduce recurrence rates treating microscopic disease, and (3.) to provide a total body disease staging and facilitate follow-up (87). Indeed, once all residual normal thyroid tissue is destroyed by RAI-T (i.e. remnant ablation), the positive predictive value of serum Tg is improved.

RAI-T use is not recommended or should be performed at low activities after recombinant human TSH stimulation only in selected cases of low-risk DTC (9, 88). No benefit in terms of survival is expected with this treatment and the benefits in terms of reduced risk of recurrence, low by definition, are controversial (87). Several retrospective reports and cohort studies found no significant difference in RAI-T and no RAI-T low-risk DTC in terms of disease recurrence (87, 89). The results of two European randomized trials ESTIMABL2 (trial number: NCT01837745) and IoN study (trial number: NCT01398085) will probably shed light on this issue.

TSH-stimulated Tg is not informative in DTC patients treated with total thyroidectomy without RAI-T, as it will increase to >1 ng/mL in half of the cases due to normal thyroid remnants (42) and is generally not recommended (9). A cutoff of stimulated Tg 2 ng/mL for these patients has been proposed by some authors, but no validated cutoff is available to date (90). Also the interpretation of punctual serum Tg values on levothyroxine treatment can be challenging in these patients. Indeed, detectable Tg on levothyroxine treatment is found in about 40% of the patients (91, 92). The trend over time of serum Tg values may be informative in these cases, and in about 80% of the cases, Tg will spontaneously decline to undetectable values (91, 92, 93) within 5 years from surgery. Nonetheless, some amounts of normal thyroid tissue may persist over time and serum Tg can persist detectable over time (94). In order to have a reliable trend, Tg should be assessed with the same assay ideally in the same laboratory (9).

The interpretation of serum Tg and TgAbs becomes even more challenging in the case of patients treated with hemithyroidectomy alone. In these patients, a cutoff of Tg <30 ng/mL to define excellent response was proposed by some authors (90), but has not been validated yet, and a stable or declining serum Tg trend over time has been proposed as a surrogate marker of disease remission. Nonetheless, neck recurrence in the contralateral lobe

or in neck lymph nodes can be found in patients with either stable, rising, or declining Tg (85). Tg should not be considered a reliable biomarker for these patients in clinical practice and neck-US should be considered the main diagnostic tool for DTC surveillance after hemithyroidectomy (95). Patients with no suspicious findings on neck US should be considered in complete remission (9) regardless of Tg values. When indeterminate findings are found on neck US, fine-needle aspiration biopsy should be considered according to size and US features and if the results will impact management as discussed before.

With regard to recurrences, some authors reported the occurrence of late recurrences in low-risk patients with a peak at 12 years after primary treatment, with a hazard rate of recurrence slightly above 0.01 (96). This was not paralleled by an increase in thyroid cancer mortality. It is worth noting that most patients of this cohort were treated with less than total thyroidectomy and did not received RAI-T (98.5%) (96).

Regardless of all these considerations, all patients treated with total thyroidectomy and at least one-third of patients treated with hemithyroidectomy will need thyroid hormone replacement therapy. Lifelong yearly TSH assessment is mandatory for post-surgical hypothyroidism surveillance. The optimal TSH target depends on the response to treatment (Fig. 1).

In the absence of high quality data on surveillance outcomes, no firm conclusions can be drawn on the optimal timing for thyroid cancer surveillance end. Nonetheless, high intensity follow-up is unlikely to impact survival in low-risk patients (97).

A proposal based on author opinion (L L) of follow-up tools and schedule intensity depending on the kind of initial treatment performed and the ongoing risk assessment is summarized in Fig. 1.

Patients that fulfill the criteria for excellent response, treated with total thyroidectomy with or without RAI-T, should be followed-up with periodic (12 to 24 months) Tg on levothyroxine treatment and TgAb assessments. The repetition of neck US may be considered after 3 to 5 years, if ever, in those patients that have persistently undetectable Tg values. The occurrence of DTC recurrence in the absence of serum biomarkers alteration is exceptional in these low-risk DTC (37).

After 5 years from primary treatment, the follow-up of these patients in a tertiary care center is probably not mandatory. Lifelong yearly TSH assessment should be performed in a primary care setting (e.g. by the general practitioner). Coupling this surveillance with serum Tg

Figure 1

Low-risk DTC follow-up: schematic proposal based on 'pros' author's opinion. AbTg, anti thyroglobulin antibodies; BIR, biochemical-incomplete response; FNAb, fine-needle aspiration biopsy; f-up, follow-up; HemiT, hemithyroidectomy; Ind, indeterminate response; LT4, levothyroxine; mo, months; neck US, neck ultrasonography; SD, structural disease; Tg, thyroglobulin; Tg/LT4, thyroglobulin under levothyroxine treatment; Tg/TSH, thyroglobulin under TSH stimulation; TT, total thyroidectomy; RAI-T, radioiodine treatment; yr, year.

on levothyroxine treatment and TgAb assessment every 12–24 months can be considered. This strategy might allow the diagnosis of the rare cases of late recurrence (notably in not RAI-T treated patients).

A Canadian study of low-risk DTC patients demonstrated that surveillance performed in a primary care setting was less expensive and more effective in reaching TSH target than tertiary care surveillance with a comparable rate of recurrences diagnosed (1.1% in primary care and 1.3% in tertiary care) (98). A randomized trial of surveillance in tertiary care centers vs primary care (assisted with telemedicine) is ongoing in Brazil (trial number: NCT03794375). The study rationale makes the hypothesis that the two follow-up strategies are equivalent.

Patients with a biochemical-incomplete or indeterminate response should be periodically followed in a specialized setting with serum Tg on levothyroxine treatment, TgAb and neckUS. Whole body imaging should be considered in case of rising trend of serum markers and in FTC and HCC histotypes. In those patients in whom excellent response is achieved, the surveillance could be pursued in a primary care setting with serum markers surveillance.

Patients treated with hemithyroidectomy alone with no abnormal finding at neckUS, neckUS surveillance should be performed every 12 to 24 months for the first 5 years after primary treatment. Further neckUS surveillance might be performed at 3–5 years intervals in a primary care setting.

Conclusion

Better awareness of DTC prognosis and the availability of sensitive diagnostic tools allowed treatment de-escalation in low-risk DTC.

This can paradoxically result in more intensive care of lower risk tumors, as observed in the case of active surveillance of very low-risk microPTCs that require a specialized follow-up and an increased number of patients with Tg in the biochemical-incomplete or indeterminate range because of the persistence of normal thyroid remnants. The development of alternative biomarkers and more precise prognostic tools might solve this paradox in the future (99).

Anyway, the vast majority of low DTC patients will not experience recurrence and will fulfill excellent response criteria. The long-term surveillance of these patients after the first 5 years after primary treatment may be

performed in a primary care setting, reducing healthcare costs and virtually eliminating any risk of missing recurrence diagnosis.

'Follow-up of low-risk DTC patients: can we stop follow-up after 5 years of complete remission?' Cons

The follow-up time of cancer patients is affected mainly by the natural history and prognosis of the disease. For example, a 5-year follow-up may be sufficient for a lung cancer trial to capture enough events of interest, but this follow-up duration may deliver insufficient information in breast cancer, with this malignancy's better prognosis and survival (97).

Differentiated thyroid cancer (DTC) is considered to be a slow-growing malignancy with a low mortality rate, but a relatively high recurrence rate (12, 48, 98). Since much literature suggests that the majority of recurrences occur within the first 5 years of observation (88, 99, 100), in most DTC studies, median follow-up falls approximately in this interval. This element of study design means that half of the patients are observed for more than 5 years, but the other half are observed for less than 5 years, sometimes even for less than 1 year. If the number of patients who reach a specific length of observation (e.g., 5–10 years) is low in relation to the number of patients that started the study, the results of the study may not be reliable. In the majority of DTC studies, the number of patients who are observed for more than 5 years, and especially for more than 10 years, is relatively low (Table 1). In other words, in the majority of DTC studies, we cannot be sure about rates of recurrence after follow-up longer than 5–10 years. This is even more complicated by the fact that, in majority of studies, low, intermediate, and sometimes even high risk patients are studied together (Table 1). Although the scope of the manuscript are low-risk patients in complete remission, in many studies it is not always possible separate this specific group of patients.

Recurrence risk does not stop after 5 years of observation, even in patients with small primary tumours

Metastatic progression of cancer is a complex process, and recent models suggest that cancer recurrences represent progression of micrometastatic disease that was already present at diagnosis and not cured with initial therapy

Table 1 Summary of key studies on DTC recurrence rates regarding follow-up time and number of low-risk patients included.

Author(s)	Year of publication	Median (minimum–maximum) follow-up, years	Total number of patients	Number of low-risk patients (%)	Number and/or proportion of patients by years of follow-up categories
Mazzaferri & Jhiang (2)	1994	15.7 (0.5–47)	1355	NR	5 > 1075 (79%); 10 > 855 (63%); 15: 689 (51%)
Tuttle <i>et al.</i> (18)	2010	7 (1–15)	710	136 (19%)	5 > NR; 10 > NR
Castagna <i>et al.</i> (19)	2011	5.6	512	221 (43%)	5 > NR; 10 > NR
Vaisman <i>et al.</i> (17)	2012	10 (1–35)	506	168 (33%)	5 > NR; 10 > NR
Durante <i>et al.</i> (7)	2013	10 (5.1–20.4)	1 020	625 (61%)	5 > 100%; 10 > NR
Grogan <i>et al.</i> (3)	2013	27 (NR)	269	N0: 164 (61%); T1 & 2: 183 (68%)	5 > NR; 10 > NR
Schlumberger <i>et al.</i> (13)	2018	5.4 (0.5–9.2)	726	726 (100%)	5 > NR; 10 > 0
Dehbi <i>et al.</i> (14)	2019	6.5 (4.5–7.6)	438	N0&Nx: 367 (84%); T1&2: 333 (76%)	5 > 438 (100%); 10 > 0

NR, not reported.

(101). Small clusters of metastatic cells may survive in a quiescent state in their metastatic locus while waiting for the appropriate conditions to grow from microscopic to clinically overt disease, a period of time that is called tumour dormancy. Regulated by cancer genes, the metastatic microenvironment, and the immune system, the cancer dormancy or ‘waiting time’ for growth can vary from weeks or months (short dormancy) to even decades (long dormancy).

In DTC, although most recurrences are believed to occur within 5 years after initial diagnosis (85, 99, 100), recurrence and cause-specific mortality nonetheless can occur many years later (12, 48, 98, 102, 103), suggesting high variability in DTC dormancy.

Outside the radioiodine-refractory DTC setting, only two prospective randomised trials in patients with DTC have been published (104, 105, 106). However, neither study was designed to answer questions regarding rate or timing of disease recurrence, or need for long-term follow-up in low-risk DTC. In the HiLo trial assessing preparation methods and activities for radioiodine ablation (106), where mostly (but not only) patients with low-risk DTC were included, progression-free survival curves did not flatten out after 6 years of observation. This finding suggests that the follow-up period was insufficient to characterise timing and, ultimately, rates of recurrence and that any conclusions about these issues in this cohort should be made with caution. Although the structural recurrence rate was relatively low (21 recurrences in a sample of altogether 443 evaluable patients) after a median time of observation of 6.5 years, that rate more than doubled between the fifth and seventh years of observation, from 2.1% to 5.0%, respectively. Also notable is the fact that, in six patients, late recurrences were distant.

A similar recurrence rate after 5 years (2% in 726 patients) was observed in the ESTIMABL1 trial (105), which, like HiLo, examined preparation methods and activities for radioiodine ablation, but only in low-risk patients. However, the number of structural recurrences was low (only four patients), while the rest suffered from biochemical failure (five patients) or intermediate findings in neck US. Of note is the fact that, although median follow-up was more than 5 years in both trials, still 50% of patients were observed for fewer than 6.5 years in HiLo and fewer than 5.4 years in ESTIMABL1. A longer observation period is necessary to capture the real rate of long-term recurrence. It also should be underlined that, both in HiLo and ESTIMABL1, the low number of recurrences may be attributed not only to the biology of low-intermediate-risk or low-risk thyroid cancer but also to the efficacy of the combination of surgery plus radioiodine therapy. Additionally, according to the recent American Thyroid Association (ATA) guidelines (14), low-risk DTC patients should be treated with surgery alone, so the low number of recurrences from the previously mentioned trials, which also included radioiodine therapy, may not be generalizable to current clinical practice.

Similarly to the data from HiLo, data from retrospective studies with long follow-up suggest that, after 5–10 years of observation, there is no inflection point regarding the rate of locoregional or distant metastases (48, 103) – indeed, there is a steady increase in the recurrence rate over time. For example, data from the Mayo Clinic demonstrated that in adult patients with papillary thyroid cancer (PTC) and a low-risk MACIS score of <6, the cumulative locoregional recurrence rate increased from about 5% after 10 years to more than 20% after 30 years of observation (48). The same tendency was observed in the Mayo study regarding distant metastasis, with cumulative distant recurrence

increasing from <1% to almost 4% after 10 and 30 years of observation, respectively.

In most clinical studies, risk of death or recurrence from cancer is described by survival curves that focused on the percentage of patients who remain without treatment failure (recurrence or death) at given time points after initial interventions. On the other hand, the hazard ratio (HR) reflects the rate of failure at any instant among the remaining 'at risk' individuals. The advantage of the HR is that the measure not only describes the magnitude of the failure rate but also provides information on how that rate changes over time. In a recent study using HR (93), annual risk of PTC recurrence steadily increased until reaching a peak at 12 years after initial treatment. Thereafter, although the HR dropped, it rose again to achieve second and third peaks, 22 and 29 years after surgery, respectively. In the Dong *et al.* study (93), a comparable pattern was observed for risk of cancer death, with double peaks at 10 and 20 years after surgery. Although annual HRs differ in different ATA risk groups, even in the low-risk group with a flat annual HR during the first 10 years of observation, HR starts increasing thereafter.

The main drawback of retrospective studies in thyroid cancer is that, over the years, diagnostic and treatment approaches have changed. About 30 years ago, two main breakthroughs were introduced: serum thyroglobulin (Tg) measurement and neck ultrasonography (US); in the years since, these modalities have continued to improve in performance. One may speculate that, in the well-known study by Mazzaferri and Jhiang (12), the number of recurrences would have been lower if modern diagnostic modalities had been used to confirm complete remission, and to guide treatment of persistent disease, after initial treatment. Nevertheless, Mazzaferri and Jhiang's key observation that DTC recurrences are not infrequently diagnosed far more than 5 years after initial treatment is confirmed in some recent studies where modern follow-up methods have been already been used (10, 93, 103). On the other hand, studies that claim that most recurrences are diagnosed within 5 years after treatment have relatively low numbers of patients observed more than 5 or 10 years (106). Of note is also the fact that in the pivotal study by Tuttle *et al.* (9), in which the recurrence rate was 2%, the median time of observation was 5 years, while in a study with a cohort with similar characteristics to those of Tuttle *et al.*'s patients (10) with a median follow-up of 10 years, the recurrence rate was 12% in the whole group of low-risk patients. However, in a small subgroup of 97 patients with excellent response, there was no recurrent disease. Unfortunately, there are no data on follow-up length in this group of patients.

As alluded, the treatment approach to DTC has changed over the last decade. Historically, in the majority of studies on low-risk DTC, total thyroidectomy followed by radioiodine treatment was standard care (9, 10, 47, 107). According to the present ATA guidelines, thyroid lobectomy alone may be sufficient initial treatment for low-risk papillary and follicular carcinomas (14). This ATA recommendation is mostly, but not only, based on experience in population-level cancer databases (81, 108, 109) that do not record all factors that may be pertinent to risk group stratification, for example, lymph node micrometastases in PTC, mutational status, or vascular invasion in follicular thyroid cancer. Cervical lymph node metastases are recognized as a prognostic factor. However, little is known about the cutoff in the ratio of nodes with micrometastases to the number of nodes that would classify the patient as low-risk vs intermediate-risk (110). For that matter, little is known about the risk of recurrence in patients with lymph node micrometastases. In the near future, we can expect a growing number of patients to have been treated with less extensive surgery without radioiodine therapy, more data on recurrence risk are necessary to tailor follow-up protocols.

Currently, the only factor related to mutation status that is incorporated into risk stratification for DTC is *BRAF* mutation (14). Although *BRAF* mutation has a high prevalence, the addition of *BRAF* mutational status to established risk algorithms improves the discrimination of recurrence risk in patients undergoing total thyroidectomy for PTC (111). The relevance of *BRAF* status to outcome is to be analysed in ESTIMABL2, the follow-up study to ESTIMABL1. *TERT* promoter mutations also may help to better define the prognosis of localised thyroid cancer (112). However, the impact of *BRAF/TERT* mutation on surveillance of low-risk DTC has not yet been established.

Follow-up issues not related to recurrence risk

Early diagnosis and appropriate treatment of cancer recurrence is a main factor, but not the only factor to be considered in determining the length and intensity of follow-up of DTC.

Monitoring for side effects and secondary malignancies

Total thyroidectomy invariably, and lobectomy sometimes, result in permanent hypothyroidism. All

patients with DTC need periodic TSH evaluation to adjust treatment with L-thyroxine to optimise anti-tumour effect and minimise long-term adverse secondary effects.

The rate of complications during thyroid surgery has decreased because of better instrumentation and greater recognition of the importance of surgical expertise in thyroid and neck procedures. Laryngeal nerve injury is infrequent; however, permanent hypoparathyroidism still can be observed in 1–16% of operations, especially after total thyroidectomy and central lymph nodes dissection (113). Long-term supplementation with vitamin D analogues and oral calcium is the mainstay of life-long treatment, which should be adjusted if needed, based on periodic calcium measurement.

The overall risk of second primary malignancy (SPM) is increased for DTC survivors both in radioiodine-treated and radioiodine-untreated groups (114, 115, 116), with a latency period much longer than 5 years. Although radioiodine treatment, especially with cumulative activities higher than 7.4–11.1 GBq, is associated with some increased risk of SPM, DTC alone can also independently confer a higher risk of malignancy that may mandate surveillance (117, 118).

Economic considerations

The cost of cancer care worldwide is increasing, driven largely by the introduction of new cancer treatments and diagnostic tools. The question of cost-effectiveness is a burning issue in oncology and should be addressed regarding both therapy and surveillance. A Canadian retrospective study of mostly low-risk patients (17% with N1 disease) showed comparable results of surveillance in tertiary referral centres vs primary care settings (95), with much lower costs in the latter. The diagnostic tools used in both settings were the same – TSH and Tg measurement and neck US – but these tests were more often performed in tertiary centres. Variability in surveillance costs, however, was mostly attributed to expenditures on physician visits and patient travel. Although results of this study are of interest, the number of included patients was low (only 93 in primary care settings) and the median observation time was only about 65 months. Before shifting from tertiary referral centres to primary care, we must be sure about appropriate quality assurance regarding Tg assays and US equipment and its operation. Since serum Tg concentrations have been shown to vary by as much as 40–60% between assays (119), serum Tg should be measured by certified laboratories using validated immunoassays calibrated against Certified Reference Material, and for

longitudinal consistency, serial measurements of Tg and anti-Tg autoantibody concentrations should be performed in the same laboratory using the same assay throughout an individual's follow-up (120). These requirements could be difficult and costly to fulfill in primary care.

The previously mentioned prospective, randomised trial on follow-up of DTC patients with excellent response to treatment should answer the question on clinical, psychological, and economical consequences DTC patients surveillance in primary care center.

Savings on shifting DTC surveillance from tertiary referral centres to primary care centres may vary from high to low depending on health reimbursement policy. There are as yet no reliable published economic analyses of this issue.

Psychological considerations

Anxiety is known to be common among cancer patients, both in those cured of their disease as well as in those with metastatic involvement (22, 121). Although, from a doctor's point of view, DTC is a cancer with excellent prognosis, anxiety and fear of tumour recurrence or disease progression are an important finding in psychological interviews of patients with DTC (122, 123). Almost half of the DTC patients with an excellent prognosis will still worry about recurrence even 15 years after diagnosis (124). It also seems that, in DTC patients, perception of disease is unrelated to disease stage (125), but closely related to follow-up regimen (122), a finding that may result from patients' knowledge of the risk of recurrence even decades after the initial diagnosis. For this reason, individualised follow-up and avoidance of frequent visits may decrease anxiety in DTC patients. On the other hand, in at least some patients, cessation of follow-up after a relatively short time of 5 years may increase anxiety and create demand for psychological support. Indeed, some patients may obtain neck ultrasound and serum Tg on their own, potentially leading to false-positive results, further increase in anxiety, and unnecessary medical visits. DTC patients with fear of recurrence have been found to examine themselves to check for physical signs of recurrence (123). Also of note is the fact that recurrence of thyroid cancer is associated with significant psychological distress (126), which may be lessened if the recurrence is discovered at an earlier stage that may be more amenable to treatment.

Summary of the Con position

The limited number of published cases observed for more than 5 years following initial treatment as

well as the apparently increasing recurrence rates after that time are the main two reasons to question discontinuation of follow-up of patients with low-risk DTC after 5 years. Although relatively low, the recurrence rate seems to have no inflection point, and there are no solid data regarding the best point at which to stop patient surveillance. A prospective study with long-term follow-up – ideally more than 10 years – in all patients in a large cohort with low-risk DTC, with accurately and meticulously assessed risk factors, is essential to tailor the most appropriate surveillance regimen(s). At present, a more cautious approach would not be to continue life-long monitoring, but to progressively reduce the frequency of follow-up visits, provided that recurrence remains absent.

General conclusions

With the rapidly increasing number of early-stage DTC cases, not only adequate treatment but also patient surveillance becomes a critical issue. Paradoxically, the favourable natural history of low-risk DTC complicates formulating optimal managements guidelines, since clinical studies require large patient samples and lengthy follow-up to obtain a full picture of the event rate. The low rate of recurrence in this group of patients might justify early cessation of patient surveillance in tertiary referral care centres, to decrease economical costs and logistical and other burdens on patients. Although a growing amount of evidence supports this approach, some issues still must be addressed – that is, when is the optimal time to stop follow-up and how to organise further medical care for DTC survivors.

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