REVIEW

Lobectomy in patients with differentiated thyroid cancer: indications and follow-up

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Abstract

The extent of thyroid surgery for patients with low- and intermediate-risk differentiated thyroid carcinoma (DTC), with a primary tumour <4 cm and no extrathyroidal extension (ETE) or lymph node (LN) metastases, has shifted in a more conservative direction. However, clinicopathological risk factors, including microscopic ETE, aggressive histology, vascular invasion in papillary thyroid carcinoma (PTC) and intermediate volume of LN metastases, can only be identified after completing thyroid lobectomy. It is controversial whether patients with these risk factors should immediately undergo complete thyroidectomy and/or radioactive iodine remnant ablation or should be monitored without further treatments. Data are conflicting about the prognostic impact of these risk factors on clinical DTC outcomes. Notably, the recurrence rate in patients who underwent thyroid lobectomy is low and the few recurrences that develop during long-term follow-up can readily be detected by neck ultrasonography and treated by salvage surgery with no impact on survival. These findings suggest that a more conservative approach may be a preferred management strategy over immediate completion surgery, despite a slightly higher risk of structural recurrence. Regarding follow-up of post-lobectomy DTC patients, it is reasonable that an initial risk stratification system based on clinicohistological findings be used to guide the short-term follow-up prior to evaluating the response to initial therapy and that the dynamic risk stratification system based on the response to initial therapy be used to guide long-term follow-up.

Key Words

- thyroid
- carcinoma

Endocrine-Related Cancer
(2019) **26**, R381–R393

Introduction

Surgical treatment for a differentiated thyroid carcinoma (DTC) derived from follicular cells is a starting point of a multifaceted treatment approach. Even though DTC is generally non-aggressive and has good prognosis, choosing the extent of thyroid surgery for DTC remains controversial. The 2009 American Thyroid Association (ATA) guidelines for patients with DTC recommended total thyroidectomy as the initial surgical option for nearly all DTCs >1 cm regardless of other risk factors, based on retrospective data suggesting benefits to survival, recurrence rate, routine use of radioactive iodine (RAI)

remnant ablation and detection of recurrent disease using thyroglobulin (Tg) level (Cooper *et al.* 2009). However, recent large-scale studies found no significant survival difference between total thyroidectomy and thyroid lobectomy when adjusting for variables related to mortality risk or disease complexity and severity, besides tumour size (Nixon *et al.* 2012, Matsuzu *et al.* 2014). Recent data also show very similar clinical outcomes for thyroid lobectomy and total thyroidectomy, and the extent of initial thyroid surgery has little impact on disease-specific survival in properly selected low-to-intermediate-risk patients

whose tumours are unifocal tumours <4 cm and have no evidence of extrathyroidal extension (ETE) or lymph node (LN) metastases (Nixon *et al.* 2012, Matsuzu *et al.* 2014). Furthermore, the indication of RAI remnant ablation, a major reason for preferring total thyroidectomy, is becoming more selective in low-to-intermediate-risk DTC patients, and neck ultrasonography and serial serum Tg measurements are more preferred as follow-up tools than whole-body RAI scans requiring total thyroidectomy, even in patients treated without RAI remnant ablation (Haugen *et al.* 2016). These changes in management strategies for DTC patients, especially in low-to-intermediate-risk cases, may lower the need for total thyroidectomy and lead to revised guidelines. Therefore, changing paradigms require reassessment of the use of thyroid lobectomy.

Current indications for thyroid lobectomy and completion thyroidectomy of DTC

The 2015 ATA guidelines (Haugen *et al.* 2016) recommend thyroid lobectomy as the initial procedure for patients with DTC ≤1 cm (if surgery is chosen, instead of active surveillance), no ETE, no clinical LN metastasis, no prior

history of head and neck irradiation and no familial history of thyroid carcinoma. Initial thyroid lobectomy is also recommended for patients with DTC >1 cm and ≤4 cm (without ETE and clinical evidence of LN metastasis), low-risk PTC and follicular thyroid carcinoma (FTC). The 2015 ATA initial risk stratification system is shown in Table 1. In contrast, completion thyroidectomy is recommended for patients for whom total or near-total thyroidectomy would have been recommended if the diagnosis had been available before the initial surgery.

The National Comprehensive Cancer Network (NCCN) guidelines (Haddad *et al.* 2016) recommend that thyroid lobectomy can be an initial surgery for patients with DTC ≤4 cm without prior history of radiation exposure, distant metastasis, cervical LN metastasis or ETE upon preoperative or intraoperative evaluation. Completion thyroidectomy is recommended if the PTCs are >4 cm and show positive resection margins, gross ETE, macroscopic multifocal disease, macroscopic LN metastasis (≥3–5 involved LNs or >0.5 cm for largest dimension) or postoperative vascular invasion. It is also recommended for invasive FTCs or Hürthle cell carcinomas with extensive vascular invasion (>4 foci) and for a part of minimally invasive FTCs or Hürthle cell carcinomas (defined as a well-defined tumour

Table 1 The 2015 revised American Thyroid Association initial risk stratification system.

	Low	Intermediate	High
Tumour	No tumour invasion of locoregional tissues or structures Not aggressive histology (e.g., tall cell, hobnail variant, columnar cell carcinoma) No vascular invasion Intrathyroidal, encapsulated follicular variant of PTC Intrathyroidal, well differentiated FTC with capsular invasion and no or minimal (<4 foci) vascular invasion Intrathyroidal, PTMC, unifocal or multifocal, including BRAFV600E mutated (if known)	Microscopic invasion of tumour into the perithyroidal soft tissues Aggressive histology (e.g., tall cell, hobnail variant, columnar cell carcinoma) PTC with vascular invasion Multifocal PTMC with ETE and BRAFV600E mutated (if known)	Macroscopic invasion of tumour into the perithyroidal soft tissues (gross ETE) FTC with extensive vascular invasion (>4 foci of vascular invasion)
Node	Clinical N0 ≤5 pathologic N1 (<0.2 cm in largest dimension)	Clinical N1 >5 pathologic N1 with all involved lymph nodes <3 cm in largest dimension	Pathologic N1 with any metastatic lymph node ≥3 cm in largest dimension
Distant metastasis	No distant metastases	No distant metastases	Distant metastases
Others	All macroscopic tumour has been resected No RAI-avid metastatic foci outside the thyroid bed on the first post-treatment whole-body RAI scan	RAI-avid metastatic foci in the neck on the first post-treatment whole-body RAI scan	Incomplete tumour resection Postoperative serum Tg suggestive of distant metastases

ETE, extrathyroidal extension; FTC, follicular thyroid carcinoma; PTC, papillary thyroid carcinoma; PTMC, papillary thyroid microcarcinoma; RAI, radioactive iodine; Tg, thyroglobulin.

with microscopic capsular and/or 1–4 foci of vascular invasion) on final histopathologic examination.

The 2014 British Thyroid Association (BTA) guidelines (Perros *et al.* 2014) recommended total thyroidectomy for patients with PTCs >4cm or PTCs with multifocal disease, bilateral disease, ETE (pathologic T3 and T4), familial disease, clinically or radiologically involved LNs or distant metastases. Furthermore, it stated that the evidence is unclear for an advantage of total thyroidectomy over hemi-thyroidectomy in patients with unifocal PTCs 1–4cm in diameter and no other adverse factors such as age >45 years, ETE, familial disease, clinical or radiological evidence of LN or distant metastasis and angioinvasion. Therefore, these cases require personalised decision making and consideration of risk factors such as tumour >2cm, positive positron emission tomography, poorly differentiated component or radiation-induced cancer. Completion thyroidectomy is recommended for Hürthle cell carcinomas >1cm and for FTCs >4cm or those with adverse risk factors, such as age >45 years, wide invasiveness, LN or distant metastasis and angioinvasion.

Various preoperative and postoperative clinicopathologic features are used to predict mortality risk and to stratify the risk of structural recurrence after initial surgery. Based on each clinicopathologic variable's impact on survival and structural recurrence, they are also preoperatively used to decide the extent of initial surgical treatment for DTC, as for the international guidelines above. In predicting DTC mortality, the American Joint Committee on Cancer/Union for International Cancer Control (AJCC/UICC) Tumour Node Metastasis (TNM) staging system and the Metastasis Age Completeness of resection Invasion Size (MACIS) system provide the highest proportion of variance explained (PVE; defined as a statistical measure of how well a staging system predicts the outcome of interest) (Voutilainen *et al.* 2003, Lo *et al.* 2005, Yildirim 2005). Unfortunately, however, none of these staging systems can account for more than 5–30% (corresponding to PVE values of 0.05–0.30) of the uncertainty associated with eventual death from DTC (Voutilainen *et al.* 2003, Lo *et al.* 2005, Yildirim 2005). This inadequacy of these staging systems in predicting DTC mortality risk may be due to a lack of integration with clinicopathologic risk factors besides age, primary tumour size, ETE, location of LN metastasis and distant metastasis. Furthermore, the AJCC/TNM staging system does not adequately predict DTC recurrence (Tuttle *et al.* 2010).

Unlike these staging systems that predict DTC mortality, the 2015 ATA initial risk stratification system

predicts the risk of structural recurrence during follow-up, based on histopathologic findings obtained immediately after initial DTC surgery (Table 1). The 2015 ATA initial risk estimates incorporate detailed variables, including DTC variants, mutational status, extent of LN involvement and degree of vascular invasion in FTC. Although the comparative benefit between the 2015 ATA initial risk estimates and 2009 ATA initial risk stratification system are not established, the latter had PVE values of 19–34% (Tuttle *et al.* 2010, Castagna *et al.* 2011). Moreover, a retrospective evaluation of the 2009 ATA initial risk stratification system suggested that it may be applied even in patients treated without RAI remnant ablation as well as in patients who underwent total thyroidectomy and subsequent RAI remnant ablation (Vaisman *et al.* 2011, Durante *et al.* 2012). The variables used in this risk stratification system not only guide follow-up management, but also aid in deciding the extent of surgery for the initial surgical treatment. However, because the recurrence risk of each clinicopathologic feature within the same risk categories (low, intermediate and high) varies and risk factors can be closely interrelated, the risk factors for structural recurrence should be analysed with appropriate statistical methods to adjust for interference between variables.

Notably, risk factors within the same risk categories can be subdivided into two subgroups, according to preoperative or postoperative identification. Unlike high-risk factors that are preoperatively identified (except for extensive vascular invasion >4 foci in FTC and postoperative serum Tg level suggestive of distant metastases) and usually result in total thyroidectomy, the clinicopathologic features for the intermediate-risk category cannot be preoperatively identified. Because intermediate-risk factors identified after initial surgical treatment may be cause for completion thyroidectomy, the impact of intermediate-risk factors on structural recurrence must be reviewed and reassessed.

Impact of clinicopathologic features on survival or structural recurrence

Primary tumour size

The risk of structural recurrence is 1–2% in unifocal intrathyroidal papillary thyroid microcarcinoma (PTMC), 4–6% in multifocal intrathyroidal PTMC, 5–6% in intrathyroidal PTC 2–4cm and 8–10% in intrathyroidal PTC >4cm (Roti *et al.* 2008, Ito *et al.* 2012).

A retrospective study of 2345 patients with 1–4 cm PTC found no significant difference in disease-free survival (DFS) between a total thyroidectomy group and a thyroid lobectomy group after 1:1 propensity score matching by age, sex, primary tumour size, ETE, multifocality and cervical LN metastasis (381 patients in each group, median follow-up duration of 9.8 years) (hazard ratio (HR)=1.35 (confidence interval (CI) 0.40–1.36), $P=0.33$) (Song *et al.* 2019). Moreover, when stratified by primary tumour size, DFS did not differ between 1–2 cm tumours and 2–4 cm tumours (HR=1.57 (CI 0.75–3.25), $P=0.228$; HR=0.93 (CI 0.30–2.89), $P=0.902$, respectively) (Song *et al.* 2019). Multivariate analysis found that surgical extent had no independent role in structural recurrence (HR=1.43 (CI 0.72–2.83), $P=0.306$), emphasising that primary tumour size should not be an absolute indication for total thyroidectomy (Song *et al.* 2019). Another study analysed 2323 DTC patients with T1–T3 classifications and found that tumour size of >4 cm independently predicted DFS, locoregional failure and distant metastatic failure (Tam *et al.* 2018). In contrast, a large-scale retrospective study using the National Cancer Data Base evaluated 33,816 PTCs with 1.0–3.9 cm tumours and clinically negative LNs (30,981 receiving total thyroidectomy and 2835 undergoing thyroid lobectomy) (Rajjoub *et al.* 2018). In this study, adjusted analyses showed that total thyroidectomy for classic PTCs was associated with improved survival for 2.0–3.9 cm tumours ($P=0.03$), but not for 1.0–1.9 cm tumours ($P=0.16$). However, thyroid lobectomy and total thyroidectomy for follicular-variant PTCs had equivalent survival for 1.0–1.9 cm ($P=0.45$) and 2.0–3.9 cm ($P=0.88$) tumours (Rajjoub *et al.* 2018). Lee *et al.* retrospectively analysed 762 patients with classic PTC of 1–4 cm who underwent initial surgery (693 total thyroidectomy and 69 thyroid lobectomy, median follow-up duration of 124 months). Their multivariate analysis showed that primary tumour size >1.95 cm was an independent risk factor for structural recurrence, unlike the extent of thyroid surgery (Lee *et al.* 2018). Similarly, a retrospective multivariable analysis of 3174 DTC patients (2921 total thyroidectomy and 253 thyroid lobectomy, median follow-up duration of 12.4 years) showed that primary tumour sizes of 2.1–4.0 cm and >4.0 cm were both independent risk factors for disease-specific survival (DSS) (HR=2.44 (95% CI 1.45–4.11), $P=0.001$ and HR 7.40 (95% CI 4.02–13.63), $P<0.001$, respectively) and DFS (HR=1.97 (95% CI 1.52–2.55), $P<0.001$ and HR=2.91 (95% CI 1.92–4.42), $P<0.001$, respectively), with a primary tumour size reference of ≤ 2.0 cm (Park *et al.* 2018b).

Extrathyroidal extension

Based on the 7th AJCC/UICC TNM staging system (TNM-7), it is important to differentiate the clinical significance of minimal ETE (pathologic T3 classification, including microscopic ETE) from extensive ETE (pathologic T4 classification). The risk of structural recurrence associated with minimal ETE ranges from 3 to 9%, whereas that related to extensive ETE ranges from 23 to 40% (Lombardi *et al.* 2010, Radow sky *et al.* 2014). A retrospective analysis of 1–4 cm classic PTC patients found that the presence of extensive ETE was an independent risk factor for structural recurrence (HR=6.84 (95% CI 2.20–21.33), $P<0.001$, with a reference of no ETE), whereas minimal ETE was not (Lee *et al.* 2018). Another study also found that minimal ETE was not an independent risk factor for tumour recurrence in T1–T3 DTC patients (Tam *et al.* 2018). In addition, Park *et al.* evaluated the prognostic significance of gross ETE invading only strap muscles in 3174 DTC patients, revealing that the 10-year recurrence-free survival rate for patients with gross ETE invading only strap muscles (89.2%) was shorter than that for patients with no ETE (93.7%, $P=0.017$), but similar to that of patients with microscopic ETE (90.3%) (Park *et al.* 2018b). However, multivariable analysis showed that although extensive ETE independently predicted recurrence-free survival (HR=1.60 (95% CI 1.05–2.43), $P=0.027$), gross ETE invading only strap muscles did not (HR=1.09 (95% CI 0.71–1.69), $P=0.685$) (Park *et al.* 2018b).

The recent 8th AJCC TNM staging system (TNM-8) for DTC has removed microscopic ETE from the definition of T3 disease. These changes reflect evidence that the status of microscopic ETE as an independent prognostic factor in PTC has been increasingly questioned.

LN involvement

With respect to LN metastases, the risk of structural recurrence varies from 4% in involved LNs ≤ 5 , to 5% when all involved LNs are <0.2 cm, to 19% in involved LNs >5 , to 21% in involved LNs >10 , to 22% in clinically evident macroscopic LN metastases and 27–32% when any metastatic LN is >3 cm (Randolph *et al.* 2012, Lee *et al.* 2014). Extranodal extension of the tumour through the metastatic LN capsule is also associated with an increased risk of structural recurrent disease (Leboulleux *et al.* 2005).

Unfortunately, these risk estimates have been applied equally to N1a and N1b disease because there were insufficient data to determine each LN-related risk factor based on location within the neck. Furthermore, because

many studies evaluating LN-related risk factors of PTC included patients with both N1a and N1b classifications, the LN-related risk factors from PTCs with N1b classification might hide small but significant LN-related factors in N1a-classified patients.

Another retrospective analysis of 324 classical PTC patients classified with pathologic N1b evaluated risk factors for structural recurrence (Lee *et al.* 2016). This study separately assessed the LN-related variables (maximal diameter of metastatic LN foci, number of metastatic and retrieved LNs, metastatic LN ratio and ENE) based on the LN location (central vs lateral compartment) and found that maximal diameter of metastatic LN foci >2.0 cm (HR=1.15 (95% CI 1.06–1.25), $P=0.033$) and central metastatic LN ratio >0.42 (HR=3.35 (95% CI 1.65–6.79), $P<0.001$) were independent risk factors for locoregional recurrence. Additionally, the presence of ENE (HR=12.71 (95% CI 1.64–98.25), $P=0.015$) was an independent risk factor for distant metastasis in multivariate analyses (Lee *et al.* 2016).

Although the traditional cut-off of <0.2 cm for LN micrometastasis is commonly accepted, this definition was not derived from PTCs but from breast cancer and other solid tumours. Therefore, an appropriate cut-off of LN micrometastasis must be determined for PTC patients. Recently, retrospective multivariate analyses of 398 classic PTC patients who received total thyroidectomy with CCND and a confirmed pathologic N1a classification found that a maximal diameter of >3.5 mm for metastatic LN foci (HR=3.76 (95% CI 2.27–6.24), $P<0.001$) and ≥ 4 involved LNs (HR=3.01 (95% CI 1.82–4.92), $P<0.001$) were independent risk factors for structural recurrence, and patients with each risk factor had significantly poorer DFS rates than their counterparts without these risk factors (Lee *et al.* 2019). These results are consistent with the NCCN guidelines suggesting that macroscopic LN metastases (≥ 3 –5 involved LNs or >0.5 cm in largest dimension) adversely affect prognosis, whereas LN micrometastases (<3 –5 involved LNs and ≤ 0.5 cm in largest dimension) are associated with low structural recurrence risk (Haddad *et al.* 2016).

The revised TNM-8 entails important changes from the seventh edition for patients with DTC. One notable change is that TNM-8 categorises pathologic N1a and N1b classifications together into pathologic N1 classification; thus, N1b classification is no longer a variable for determining the final TNM stage, even though it may be debatable. In addition, age criterion for determining TNM stage is changed from 45 to 55 years. Based on these changes in the TNM-8, large number of patients with

differentiated thyroid cancer would be down-staged as compared with being staged by the TNM-7. In our opinion, because the TNM-8 staging system is newly adopted since 2018, further validation may be needed based on large scale of patients with long follow-up period.

Multifocality

Recently, a large-scale multicentre study investigated the role of tumour multifocality in clinical PTC outcomes in 2638 patients with a median follow-up time of 58 months (range: 26–107 months) at 11 medical centres in six countries, and used Surveillance, Epidemiology and End Results (SEER) data for validation. Multifocality was not a significant risk factor for structural recurrence (HR=1.13 (95% CI 0.93–1.37), $P=0.233$) in multivariate adjustment. Similarly, there was no association between multifocality and mortality in PTC variants: classical PTC, follicular-variant PTC, tall-cell PTC and PTMC (Wang *et al.* 2017). These results were reproduced in 89,680 patients with PTC in the SEER database. The findings emphasise that tumour multifocality has no independent risk prognostic value for clinical PTC outcomes, and its indiscriminate use as an independent risk factor should be avoided to prevent patient overtreatment. Other multivariate analyses also found that multifocality was not an independent risk factor of structural recurrence (Leboulleux *et al.* 2005).

Histological variants

Tall-cell variant (TCV), columnar cell variant (CCV), hobnail variant and solid variant of PTC are aggressive histologic subtypes (Haugen *et al.* 2016).

The TCV of PTC is the most common variant (incidence of 1–19.0%) and is more prevalent in males and older patients. Compared to classic PTC, TVC is associated with a higher frequency of aggressive histopathologic features at diagnosis, including large primary tumour size, multifocality, ETE, LN metastases and distant metastases (Nath & Erickson 2018). Furthermore, several studies suggest that the tall-cell histology independently affects structural recurrence and survival. In a multivariate analyses of 183 PTCs, including 19 TCVs, tall-cell histology was an independent risk factor for structural recurrence (Terry *et al.* 1994). A SEER-based study of 278 TCVs of PTC and 2522 classic PTCs found that 5-year DSS of TCVs was worse than that of classic PTCs (81.9 vs 97.8%, $P<0.001$) (Morris *et al.* 2010). Another SEER-based study also found that TCVs of PTC had shorter 5-year overall survival (80.6 vs 93.5%, $P<0.001$) after adjusting for other factors

(Kazaure *et al.* 2012). However, other contradicting multivariate analyses suggest that tall-cell histology is not an independent risk factor for structural recurrence and mortality (Michels *et al.* 2007).

The CCV of PTC can also be aggressive. Even though there are few reports, the aggressive CCVs of PTC were associated with male gender, old age, large tumour size, ETE, diffuse infiltration, laryngotracheal invasion, cervical LN metastases, distant metastases and high AJCC/UICC TNM stage. Furthermore, the DSS of patients with aggressive disease was shorter than that of patients with indolent disease (Nath & Erickson 2018).

The solid/trabecular variant of PTC accounted for approximately 37% of PTC associated with the Chernobyl nuclear disaster. This variant is more common in young patients and those with a history of ionising radiation exposure and has a higher frequency of distant metastases (usually to the lung) and less favourable prognosis. The mortality rate for this tumour in adults has been reported to be up to 10% (Nath & Erickson 2018).

The recently described hobnail variant of PTC is associated with aggressive features, including high AJCC/UICC TNM stage at presentation (stage III or IV in 62.5%), old age, vascular invasion (41.7%), LN metastases at presentation (up to 75%) and distant metastases (up to 43.5%) (Asioli *et al.* 2013, Lubitz *et al.* 2014). Furthermore, the hobnail variant of PTC is often associated with other aggressive histologic types of thyroid carcinoma and has significant mortality (33.3%) (Asioli *et al.* 2013, Lubitz *et al.* 2014).

The 2015 ATA guidelines histologically defined TCV, CCV and hobnail variants as aggressive. However, the evidence associating these aggressive histologic subtypes of PTC with unfavourable outcomes is limited, because most previous studies had small numbers of patients due to the rarity of the subtypes, except for TCV of PTC. Furthermore, no clinical studies compare prognoses of CCV and hobnail variant with that of classic PTC. More importantly, most previous studies did not adjust for major clinicopathologic factors affecting clinical outcomes.

These limitations lead to questioning whether each aggressive histologic subtype has an impact on clinical outcomes compared to classic PTC, even when other clinicopathologic factors are identical. Recently, a retrospective study compared DFS in 144 patients with three aggressive variants of PTC and 763 patients with classic PTC, after propensity score matching by age, sex, primary tumour size, LN metastasis and ETE. This study found that the group of aggressive PTC variants had

significantly lower DFS than the matched classic PTC group (HR=2.16 (95% CI 1.12–4.16), $P=0.018$) (Song *et al.* 2018). However, when TCVs and CCVs were evaluated separately, there was no significant differences in DFS and dynamic risk stratification (DRS) between patients with TCV ($n=121$) and matched classic PTC, whereas the CCV group ($n=18$) had significantly poorer DFS than the matched classic PTC group (HR=12.19 (95% CI 2.11–70.33), $P=0.005$) (Song *et al.* 2018). Furthermore, CCV was an independent risk factor for structural recurrence in multivariate analysis (HR=4.28 (95% CI 1.66–11.00) $P=0.001$), suggesting the use of individualised therapeutic approaches for each type of aggressive PTC variant (Song *et al.* 2018).

Vascular invasion

Minimally invasive FTCs (MIFTCs) with either only capsular invasion or only minor vascular invasion (1–3 foci of vascular invasion) usually have an excellent prognosis with low recurrence rates (0–3%; Goldstein *et al.* 2000, O'Neill *et al.* 2011 or 0–5%; Lang *et al.* 1986, Huang *et al.* 2011) and stratified as low risk in the 2015 ATA guidelines. In contrast, patients with MIFTC who have extensive vascular invasion (≥ 4 foci of vascular invasion) are considered to be high risk for structural recurrence because there is high risk of developing newly identified distant metastases (Collini *et al.* 2004, Huang *et al.* 2011, O'Neill *et al.* 2011, Sugino *et al.* 2011). In most previously published studies, age ≥ 45 years, primary tumour size ≥ 4 cm, presence of vascular invasion, extensive vascular invasion (≥ 4 foci), LN metastases and distant metastases at the initial diagnosis are prognostic for distant metastasis-free survival (DMFS) and DSS rates in MIFTC patients (Collini *et al.* 2004, Lo *et al.* 2005, O'Neill *et al.* 2011, Sugino *et al.* 2011). Therefore, these risk factors are widely used as criteria to recommend completion thyroidectomy to patients diagnosed with MIFTC after diagnostic thyroid lobectomy.

A previous retrospective multivariate analysis of 166 MIFTC patients with a median follow-up period of 103.5 months found that vascular invasion (HR=29.06 (95% CI 3.06–209.08), $P=0.015$) and extensive vascular invasion (≥ 4 foci) (HR=40.57 (95% CI 2.09–789.13), $P=0.014$) were the only independent risk factors for distant metastasis (Lee *et al.* 2017). However, surgical extent (HR=1.57 (95% CI 0.29–8.47), $P=0.598$) and RAI remnant ablation or lack thereof (HR=2.73 (95% CI 0.44–17.04), $P=0.284$) were not independent risk factors for distant metastasis, demonstrating that further

treatment after initial thyroid lobectomy did not prevent distant metastasis at follow-up (Lee *et al.* 2017).

In PTC, the prognostic impact of vascular invasion is controversial. A multivariate analysis of 412 PTC patients matched for age, gender, histologic variants and TNM stage found that vascular invasion (HR=3.63 (95% CI 1.47–8.94), $P=0.005$) was an independent risk factor for distant metastasis, and patients with vascular invasion had significantly shorter DMFS ($P<0.001$) (Cao *et al.* 2016). In contrast, another multivariate analysis of 698 DTC patients showed that vascular invasion was significantly associated with a primary tumour size of >4.0cm, ETE, distant metastasis and RAI treatment, but was not an independent predictor of DMFS (Wreesmann *et al.* 2015).

B-type Raf kinase (*BRAF* V600E) mutation status

To resolve conflicts from various single-centre studies, several meta-analyses and multicentre studies assessed the prognostic significance of the *BRAF*V600E mutation. In a systematic review and meta-analysis of 2470 PTC patients from nine different countries, risk ratios in *BRAF* mutation-positive patients were 1.93 (95% CI 1.61–2.32, $P<0.00001$) for structural recurrence, 1.32 (95% CI 1.20–1.45, $P<0.00001$) for LN metastasis, 1.71 (95% CI 1.50–1.94, $P<0.00001$) for ETE, 0.95 (95% CI 0.63–1.44, $P=0.82$) for distant metastasis and 1.70 (95% CI 1.45–1.99, $P<0.00001$) for advanced stage III/IV (Tufano *et al.* 2012). Another meta-analysis of 2247 PTMC patients revealed that patients with a *BRAF*V600E mutation had a higher likelihood of structural recurrence (odds ratio (OR) 2.09 (95% CI 1.31–3.33), $P=0.002$) (Chen *et al.* 2016). However, because the *BRAF*V600E mutation is tightly linked to conventional risk factors for recurrent disease, it is difficult to determine the proportion of risk attributable to the *BRAF* mutation versus other clinicopathologic features. Several studies (Xing *et al.* 2005, Elisei *et al.* 2012), but not all (Kim *et al.* 2006, Fernandez *et al.* 2013), demonstrated that *BRAF*V600E mutation is an independent predictor for risk of structural recurrence in multivariate analysis. A large multicentre pooled-data evaluation of 2099 patients found that the *BRAF*V600E mutation was significantly associated with the risk of structural recurrence in PTCs (20.9 vs 11.6%, HR 1.38 (95% CI 1.07–1.80), $P<0.001$ after adjustment for age, sex, primary tumour size, ETE, LN metastasis, multifocality, and PTC subtypes).

This significant association was also found in patients with stage I or II, PTMC and subtypes of PTC (classic- or follicular-variant) (Xing *et al.* 2015). Another retrospective multicentre study of 1849 PTC patients from 13 centres in seven countries investigated the relationship between *BRAF*V600E mutation and PTC-related mortality (Xing *et al.* 2013). The overall mortality for PTC cases in *BRAF*V600E-positive patients was 5.3% (45/845; 95% CI, 3.9–7.1%) vs 1.1% (11/1004; 95% CI, 0.5–2.0%) in mutation-negative patients with PTC after adjustment for age and sex (HR 2.66 (95% CI 1.30–5.43), $P<0.001$) (Xing *et al.* 2013). However, when also adjusted for LN metastasis, ETE and distant metastasis, the association of *BRAF*V600E with mortality was no longer statistically significant (for all PTC: HR, 1.21 (95% CI 0.53–2.76); for classic PTC: HR 1.51 (95% CI 0.50–4.57)); however, *BRAF*V600E-positive patients had significantly poorer survival in each analysis (Xing *et al.* 2013).

Recent data also suggest that thyroid carcinoma is likely to be aggressive when a *BRAF* mutation is concurrent with other oncogenic mutations, including *TERT* promoter, *PIK3CA* or *TP53* mutation (Ricarte-Filho *et al.* 2009, Xing *et al.* 2014). These types of combinations of mutations are expected to be more specific markers of unfavourable PTC outcomes (Haugen *et al.* 2016). Based on these data, it appears that the *BRAF* status alone is not sufficient to substantially contribute to risk stratification for most patients. Therefore, *BRAF* mutational evaluation for initial postoperative risk stratification in DTC is not routinely recommended. The *BRAF*V600E mutational status can be most helpful for deciding initial surgical extent or postoperative management when it is presented with other concurrent clinicopathological risk factors for structural recurrence.

Proposed indications for thyroid lobectomy for DTC

Based on a review of the impacts of various clinicopathologic features on structural recurrence or survival, we present proposed indications for thyroid lobectomy for DTC in Table 2. Variables classified into indications for thyroid lobectomy had profoundly conflicting data from previous studies or lacked evidence due to insufficient data. Thus, these classifications required larger scale multinational and multicentre study with longer follow-up periods.

The most confusing data were that regarding LN involvement. Most international guidelines do not

Table 2 Proposed indications and contraindications of thyroid lobectomy for differentiated thyroid carcinoma.

	Absolute indications	Relative indications	Contraindications
Completion thyroidectomy after thyroid lobectomy	Not recommended	Personalised decision making regarding other concurrent clinicopathologic risk factors	Recommended
Primary tumour size	≤1 cm (if patients choose surgery) and >1 cm and ≤2 cm	>2 cm and ≤4 cm	>4 cm
ETE	No	Minimal (microscopic or only invasion of strap muscle)	Extensive (T4)
LN involvement	Clinical N0 and number of metastatic LNs <3 (or 5) and maximal diameter of metastatic foci of LNs ≤0.35 (or 0.5) cm and metastatic LN ratio ≤0.4	Number of metastatic LNs ≥3 (or 5) or maximal diameter of metastatic foci of LNs >0.35 (or 0.5) cm and ≤2 (or 3) cm or metastatic LN ratio >0.4 (if compartment-oriented LN dissection was performed)	Clinical N1 or maximal diameter of metastatic foci of LNs >2 (or 3) cm
Multifocality	Absent or present	–	–
Histologic variants	Classic	Tall cell, Columnar cell, Hobnail	–
Vascular invasion	In FTC, absent or <4 foci of vascular invasion In PTC, absent	In PTC, present	In FTC, ≥4 foci of vascular invasion –
<i>BRAF</i> V600E mutation	Wild	Mutant	–

ETE, extrathyroidal extension; FTC, follicular thyroid carcinoma; LN, lymph node; PTC, papillary thyroid carcinoma.

recommend prophylactic central LN dissection without evidence of LN metastasis upon physical examination or preoperative imaging studies. Therefore, it is difficult to evaluate the significance of microscopic or low-volume LN metastasis based on a large patient cohort. Furthermore, the extent and skill of central LN dissection differ between institutions and surgeons. Therefore, the significance and general applicability of data for LN-related risk factors for structural recurrence and survival must be limited, because it was mostly based on single-centre studies.

As described earlier, the management strategies for DTC patients, especially low- to intermediate-risk patients, are undergoing change. The indications for RAI remnant ablation are shifting more selectively towards low-to-intermediate-risk DTC patients, and follow-up tools are now shifting away from whole-body RAI scan and towards neck ultrasonography and serial serum Tg measurements, even in patients not treated with RAI remnant ablation. These changes decrease the use of total thyroidectomy in low-to-intermediate-risk DTC patients.

DTC patients treated with lobectomy (unilateral lobectomy and/or isthmusectomy) and no RAI have excellent outcomes (Durante *et al.* 2012, Vaisman *et al.* 2013, Matsuzu *et al.* 2014). Recurrence rates for ATA low-to-intermediate-risk patients selected for thyroid lobectomy were 4.1–5.7% in the thyroid remnant, 1–8.5% in regional LNs, 0–3.2% in distant metastatic sites and 0–2.0% mortality (Durante *et al.* 2012, Vaisman *et al.* 2013, Matsuzu *et al.* 2014). Over a median follow-up period that

ranged from 5–10 years, structural recurrence was found in less than 1–2% of ATA low-risk patients and 8% of ATA intermediate-risk patients, who underwent thyroid surgery without RAI ablation as initial therapy (Vaisman *et al.* 2011, Durante *et al.* 2012).

The few recurrences that develop during long-term follow-up are readily detected by neck ultrasonography and treated without affecting survival, because salvage therapy is effective in the minority of patients that experience recurrence after thyroid lobectomy (Vaisman *et al.* 2011, Nixon *et al.* 2012, Matsuzu *et al.* 2014). Therefore, although some controversial clinicopathologic features may be found after thyroid lobectomy, a more conservative management approach might be a reasonable alternative to immediate completion surgery, despite the slightly higher risk of structural recurrence.

It has been well known that the surgical morbidity associated with thyroid surgery, including recurrent laryngeal nerve injury and hypoparathyroidism, is absolutely less in patients undergoing thyroid lobectomy than in those undergoing total thyroidectomy. In addition, institutional studies examining outcomes following thyroidectomy by high-volume surgeons have been published demonstrating overall safety. Sosa *et al.* found a strong association between higher surgeon volume and favourable patient outcomes, especially with regard to recurrent laryngeal nerve injury and wound complications (Sosa *et al.* 1998). In a recent study of patients undergoing thyroidectomy in the Health Care

Utilization Project Nationwide Inpatient Sample (HCUP-NIS), high-volume surgeons had the lowest complication rates for patients who underwent total thyroidectomy for cancer at 7.5%; intermediate-volume surgeons had a rate of 13.4% and low-volume surgeons 18.9% ($P < 0.001$) (Kandil *et al.* 2013). Therefore, it may be reasonable to consider sending patients with more extensive disease and concern for grossly invasive disease to a high-volume surgeon experienced in the management of advanced thyroid cancer.

Short-term follow-up strategies of DTC patients undergoing thyroid lobectomy

The intensity and frequency of short-term follow-up strategies for DTC patients treated solely with thyroid lobectomy are not well established, likely because most previous international guidelines recommended total thyroidectomy for nearly all PTCs >1 cm. Therefore, there are few data available for patients with PTCs who underwent thyroid lobectomy, especially those with PTCs measuring 1–4 cm.

The 2014 BTA guidelines (Perros *et al.* 2014) suggest that patients who have not received RAI remnant ablation do not require TSH suppression so long as TSH levels are maintained in the low-normal range (0.3–2.0 mU/L). For patients who underwent thyroid lobectomy for a tumour ≤ 1 cm and have no other adverse factors as mentioned earlier, TSH suppression or long-term follow-up is not recommended. The exception is annual thyroid function testing, and replacement treatment with levothyroxine may be required in patients with overt hypothyroidism. Furthermore, these guidelines do not recommend TSH suppression even for thyroid lobectomy patients with low-risk tumours (between 1–4 cm), and instead recommend personalised decision making that considers additional risk factors (>2 cm, positron emission tomography positive, poorly differentiated component or radiation-induced cancer) to determine frequency and duration of follow-up. For low-risk patients with no evidence of disease, and only annual measurement of serum Tg/anti-Tg antibody and TSH is recommended.

The NCCN guidelines (Haddad *et al.* 2016) recommend measuring Tg and anti-Tg antibody 6–12 weeks after initial surgery and assessing trend patterns in thyroid lobectomy patients. Physical examination, TSH and Tg/anti-Tg antibody measurements are recommended 6 and 12 months after the initial operation, and annually

thereafter if patients are disease free. Periodic neck ultrasound is recommended only for patients with reasonable suspicion of structural recurrence. TSH suppression therapy with levothyroxine is theoretically recommended to maintain low TSH levels, although data to allow for precise specification of the appropriate target TSH levels is lacking. In general, target TSH levels are either slightly below or slightly above the lower limit of the reference range for disease-free patients who are at low risk of structural recurrence. However, maintaining TSH levels at 0.1–0.5 mU/L is recommended for low-risk patients with biochemical evidence but no structural evidence of disease. Patients who remain disease free for several years can maintain TSH levels within the reference range.

The 2015 ATA guidelines (Haugen *et al.* 2016) recommend deciding postoperative management during the early postoperative period (within 2 years of initial treatment) based on the ATA initial risk estimates, which specify initial target TSH levels as 0.1–0.5 mU/L for ATA intermediate-risk patients and 0.5–2.0 mU/L for ATA low-risk patients, assuming patients who have undergone thyroid lobectomy while monitoring for structural recurrence by neck ultrasonography and measuring serum Tg/anti-Tg antibody and TSH. However, a retrospective multivariate analysis of 1047 PTC patients with a median follow-up duration of 107 months (range: 13–216 months) demonstrated that structural recurrence only occurred in 42 patients (4.0%); additionally, TSH levels at 1 year after initial surgery (HR 1.15 (95% CI 1.03–1.28), $P = 0.013$) were an independent risk factor for structural recurrence and significantly associated with DFS ($P = 0.012$) (Park *et al.* 2018a). The cut-off of TSH levels affecting structural recurrence was 1.85 mU/L, calculated by receiver-operating curve (Park *et al.* 2018a). Interestingly, this study found that ATA risk category (low- or intermediate-risk) was not associated with structural recurrence by either univariate or multivariate analysis. Target TSH values of <1.85 mU/L during the early postoperative period are within the target TSH levels (0.5–2.0 mU/L) recommended for ATA low-risk patients after thyroid lobectomy, but higher than that (0.1–0.5 mU/L) recommended for ATA intermediate-risk patients. Although further studies are needed to confirm target TSH levels after thyroid lobectomy, these results suggest that ATA intermediate-risk patients, like ATA low-risk patients, can be monitored using TSH levels at a low-normal range during the early postoperative period prior to evaluating initial therapy responses.

Long-term follow-up strategies for DTC patients undergoing thyroid lobectomy

The ATA initial risk stratification systems can guide initial treatment, including the extent of surgery, the need for RAI remnant ablation and TSH suppression, and the intensity and type of early follow-up studies. However, these systems only provide static representations of risk based on data available at initial treatment, and do not include data obtained during follow-up to allow evaluation of the response to initial therapy. Recently, a DRS system based on the response to initial therapy (excellent, indeterminate, biochemical incomplete or structural incomplete) has been proposed to more accurately predict long-term outcomes and to guide follow-up strategies by reclassifying initial risk estimates only based on histopathologic findings. Each response-to-therapy category of DRS is determined by detailed definitions according to the initial treatments, using data obtained during the first 2 years after initial treatment (Table 3). The DRS system has mainly been validated in patients treated with total thyroidectomy and RAI remnant ablation, demonstrating that the capability of the DRS system (PVE, 62–84%) to predict long-term

structural recurrence has more statistical power than the ATA initial risk stratification system (PVE, 25–34%) (Tuttle *et al.* 2010, Castagna *et al.* 2011, Haugen *et al.* 2016).

While the DRS is focused on patients undergoing total thyroidectomy and subsequent RAI remnant ablation, it can also be applied to patients with DTC undergoing thyroid lobectomy or total thyroidectomy without RAI remnant ablation, by using modified definitions of the response-to-therapy categories (Table 3). Recent studies showed that the DRS system was effective for modifying the initial risk estimates of structural recurrence/persistence and provided valuable information for predicting structural recurrence even in thyroid lobectomy patients (Vaisman *et al.* 2013, Momesso *et al.* 2014).

Retrospective studies compared the capability of the DRS in predicting long-term structural recurrence with that of the ATA initial risk estimates, with regard to their PVEs. One study of 619 PTC patients treated with thyroid lobectomy revealed that the PVE of the DRS system (32.4%) was higher than that of the ATA risk estimates (29.4%), but lower than what was described for patients treated with total thyroidectomy with RAI remnant ablation (Cho *et al.* 2018).

Table 3 Definition of each response to initial therapy in dynamic risk stratification system using data from within 2 years or at any time after surgery.

Response to therapy category	Definitions		
	Total thyroidectomy with RAI remnant ablation	Total thyroidectomy without RAI remnant ablation	Thyroid lobectomy alone
Excellent	Non-stimulated Tg <0.2 ng/mL or stimulated Tg <1.0 ng/mL	Non-stimulated Tg <0.2 ng/mL or stimulated Tg <2.0 ng/mL	Non-stimulated Tg <30 ng/mL and undetectable anti-TgAb levels
Indeterminate	and undetectable anti-TgAb levels and negative imaging	and undetectable anti-TgAb levels and negative imaging	and negative imaging
	Non-stimulated Tg 0.2–1 ng/mL or stimulated Tg 1–10 ng/mL or stable or declining anti-TgAb levels in the absence of structural or functional disease or nonspecific findings in imaging studies or faint uptake in thyroid bed on RAI scanning	Non-stimulated Tg 0.2–5.0 ng/mL or stimulated Tg 2–10 ng/mL or stable or declining anti-TgAb levels in the absence of structural or functional disease or nonspecific findings in imaging studies or faint uptake in thyroid bed on RAI scanning	Stable or declining anti-TgAb levels in the absence of structural or functional disease or nonspecific findings in imaging studies
Biochemical incomplete	Non-stimulated (suppressed) Tg >1 ng/mL or stimulated Tg >10 ng/mL	Non-stimulated (suppressed) Tg >5 ng/mL or stimulated Tg >10 ng/mL	Non-stimulated Tg >30 ng/mL or increasing Tg values with similar TSH levels
Structural incomplete	or rising anti-TgAb levels and negative imaging Structural or functional evidence of disease regardless of Tg or anti-TgAb levels	or rising anti-TgAb levels and negative imaging Structural or functional evidence of disease regardless of Tg or anti-TgAb levels	or rising anti-TgAb levels and negative imaging Structural or functional evidence of disease regardless of Tg or anti-TgAb levels

RAI, radioactive iodine; Tg, thyroglobulin; TgAb, Tg antibody.

Another study analysed 357 DTC patients receiving thyroid lobectomy or total thyroidectomy without RAI remnant ablation, finding that the PVE of the DRS system (12.2%) was much higher than that of the ATA risk estimates (0.74%), and the risk of recurrent/persistent disease was significantly greater in the biochemical-incomplete response (HR=20.8 (95% CI 4.0–107.1), $P<0.001$) and structural-incomplete response group (HR=243.3 (95% CI 46.5–1272.1), $P<0.001$) than in the excellent response group (Park *et al.* 2017).

When considering these results, it makes sense that long-term follow-up strategies, including monitoring target TSH levels, are guided by the DRS based on the response to initial therapy rather than ATA initial risk estimates. Follow-up after thyroid lobectomy relies on neck ultrasonography with non-stimulated serum Tg/anti-Tg antibodies at 6–12-month intervals after initial therapy. If these follow-ups are unremarkable, non-stimulated serum Tg/anti-Tg antibodies can be obtained annually and neck ultrasonography performed at 3–5-year intervals. The TSH target is recommended to be maintained between 0.5–2.0 mU/L for patients with an excellent initial therapy response, 0.5–1.0 mU/L for patients with an indeterminate or biochemically incomplete response and about 0.1 mU/L for patients with a structurally incomplete response.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this review.

Funding

This work did not receive any specific grant from any funding agency in the public, commercial, or not-for-profit sector.

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Received in final form 12 April 2019

Accepted 24 April 2019

Accepted Preprint published online 24 April 2019