Review Article

Total thyroidectomy versus thyroid lobectomy in the treatment of papillary carcinoma

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Abstract: Extent of thyroidectomy for papillary thyroid carcinoma is still matter of debate. Indeed, recently, international guidelines endorsed thyroid lobectomy as initial surgical approach for low risk, small medium-sized (T1–T2), N0 papillary thyroid carcinoma in absence of extrathyroidal extension. When dealing with a conservative surgery for oncologic disease is of utmost importance to exclude effectively more advanced disease, which could benefit from a more aggressive initial operation. However, in the setting of surgery for papillary thyroid carcinoma, despite an accurate preoperative work up could led to identify some suspicious characteristics as macroscopic evidence of multifocality or extrathyroidal extension, and/or evidence of lateral neck lymph node metastases, it is difficult to reliably assess the central neck nodal status both pre- and intra-operatively. Frozen section examination of the central neck nodes ipsilateral to the side of the tumor has been proposed in patients scheduled for thyroid lobectomy, in order to modulate the extension of both thyroidectomy and central neck dissection. Future molecular and genetic evidences are needed to establish high-risk patients with small papillary thyroid carcinoma in which thyroid lobectomy could be not and adequate surgical treatment.

Keywords: Papillary thyroid carcinoma (PTC); total thyroidectomy (TT); thyroid lobectomy (TL); extension of thyroidectomy; personalised medicine

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Introduction

The adequate extent of surgical management of papillary thyroid carcinoma (PTC) is still matter of debate, since several authors and some evidence support a more conservative surgical strategy in order to minimize the potential morbidity resulting from supposed overtreatment (1-5). While the previous American Thyroid Association (ATA) guidelines (6) considered total thyroidectomy (TT) as a standard of care for PTC >1 cm, the last version of ATA guidelines (7) endorses thyroid lobectomy (TL) as initial surgical approach for low risk, small medium-sized (T1–T2), N0 PTC in absence of extra-thyroidal extension. Similarly, the British Thyroid Association Guidelines for the Management of Thyroid Cancer (8) and the Italian Consensus on diagnosis and treatment of differentiated thyroid cancer (9) proposed TL in selected cases of PTC.

The trend towards a conservative surgical approach in the treatment of selected cases of PTC was mainly due to the finding of large population studies that demonstrate no benefits of TT over TL in terms of overall survival (1,10-13). However, it can be argued that overall survival alone could

not be the best indicator of adequacy of initial surgical treatment and data are lacking about disease free survival and disease specific overall survival. Moreover, it's well known that a not negligible number of PTC patients could experience recurrence and could require additional/s surgical treatment/s (14-16), resulting in worse quality of life (17) and possibly in technical demanding surgical re-exploration (18,19).

However, the long-term clinical outcome, in terms of remnant-thyroid recurrence-free survival, regional-lymph-node recurrence-free survival and distant-recurrence-free survival, of PTC patients underwent lobectomy plus central and/or lateral neck dissection, was demonstrated to be favourable in selected cases: age <45 years, tumor size ≤40 mm, no clinical lymph node metastases, no extra-thyroidal invasion (10).

In the last version of ATA guidelines (7), TT remains the preferable treatment option for tumors >4 or <4 cm with high-risk features. It's well known that high-risk features (such family history of thyroid carcinoma, prior neck irradiation, multifocality, extrathyroidal extension and central and/or lateral lymph node neck involvement) require more extended surgical resections (i.e., TT with/without lymph node dissection) (7).

Since prospective data on outcomes following TL with curative intent for low-risk T1–T2 PTC are lacking, the adequate extent of initial operation in these cases remains controversial. In this regard, current guidelines focused on risk stratification of PTC patients to modulate the treatment strategy (7-9). Indeed, the choice of initial surgical treatment plays an important role and it should not rely on tumor size alone (20-22). However, most of the prognostic factors for the risk stratification of PTC patients are not preoperatively available (microscopic multifocality and/or extra-thyroidal extension, central neck nodal status, aggressive histologic variant, etc.) (7-9,23,24), potentially leading to a postoperative upstaging to a higher-risk category after a limited thyroid resection (i.e., TL) in up to 40% of cases (20).

The correct stratification of the preoperative risk for each PTC patient is mandatory in order to tailor the correct extent of initial surgical approach.

Risk stratification: preoperative assessment

Medical history

The last ATA guidelines states that pertinent historical higher risk features must be investigated, such as a rapid growth of nodule, sudden swallowing dysfunction or dysphonia (7).

In addition, many pertinent information can be acquired at the time of patients' interview. Authors agree that an age ≥45 years, female sex, familial history of thyroid cancer and previous cervical irradiation, are predisposing factors of developing thyroid cancer (7,10,25,26).

Thyroid cancer has been shown to have a higher incidence in patients with age ≥45 years and in several staging systems, age of 45 years is used as cut-off between low risk and high risk for develop thyroid cancer (7,26). Ganly *et al.* (27) analysed a cohort of 3,664 patients affected by differentiated thyroid cancer treated at Memorial Sloan Kettering Cancer Center over 25 years [1985–2010] to determine the significance of age at diagnosis. The authors conclude that there is no specific cut-off age able to stratify the cancer risk for PTC patients. However, the mortality due to PTC increases progressively with advancing age (27). Recently, the latest 8th edition of TNM introduced a change in age cut-off from 45 to 55 years as threshold for high risk of disease-specific mortality (28). Moreover, Kim *et al.* (29) evaluated the disease-specific survival (DSS) in a cohort study of 6,333 PTC patients who underwent surgery at two tertiary referral centres over 20 years, reporting that the cut-off age of 55 years is more appropriate for TNM staging to achieve better predictability for DSS (29).

The incidence of thyroid cancer is higher in women than in men (30,31). In the case of PTC, the sex ratio remained constant over the time, across countries worldwide (30,31). Kilfoy *et al.* (30), examined data from Cancer Incidence in Five Continents (CI5) over 3 decades [1973–2002] from 19 populations worldwide showing a consistent female-to-male ratio (3-to-1 thyroid cancer incidence) within most of the countries. A recent epidemiological review on 77,276 patients from SEER-9 Registry Database over the last 4 decades confirm this data, demonstrating a distinct higher incidence of thyroid cancer in female patients (75.3% *vs.* 24.7%) (32).

Familial history of thyroid cancer in a first degree relatives must be investigated (7); indeed, 5–10% of patient affected by PTC have a familial occurrence (7). Similarly, Myung *et al.* (33) in a hospital-based case-control study over 802 thyroid cancer cases out of 34,211 patients screened from the Cancer Screenee over one decade, found that female sex and family history of thyroid cancer are risk factors for developing thyroid cancer (33).

History of radiation exposure in young age (head and neck irradiation, total body radiation), has always been

considered as a risk factor for developing thyroid cancer, and in particular for PTC onset (7). The risk is higher if radiation exposure occurs in I or II decade, and significantly decreases in patients >20 years (34,35). Veiga *et al.* (36) published a pooled analysis of more recent literature regarding radiation exposure in patients under age 20 years at the time of first irradiation. The analysis included 1,070 patients with thyroid cancer, and identified a consistent risk of develop thyroid cancer across a range of external radiation through 2–4 Gy, then levelling and declining above 30 Gy approximately. Radiogenic effects occurred for both papillary and non-papillary tumours. Data supported an association for thyroid radiation dose and use of chemotherapy for a primary cancer in childhood. In addition, authors underlined that significant thyroid cancer risk appeared within 5 to 10 years from radiation exposure and remained elevated for many decades (36).

Neck ultrasound (US)

High-resolution US is a standard preoperative study in differentiated thyroid carcinoma, as reported in the most recent guidelines (7-9). In 2004, Reiners *et al.* (37) published the Papillon study US, a mass screening on 96,278 patients, reporting that US (7.5 MHz probe) was able to detect thyroid nodules in 33% of patients. Using the 13 MHz technology, Guth *et al.* (38) report a substantially higher prevalence of thyroid nodules (68%), potentially contributing to the increasing incidence of thyroid cancer (39).

The preoperative US scan is able to identify several features that can guide the correct surgical strategy:

- Presence of clinical multifocal disease: an accurate US scan potentially can provide information about the extension and dimension of clinical multifocal disease (unilateral or bilateral; micro- or macro-contralateral nodule/s). The prognostic role of multifocality has been underlined by a recent meta-analysis that confirmed the association between multifocality and disease progression features such as lymph node metastases (P<0.001), extrathyroidal extension (P<0.001) and recurrence (P<0.001) (40).
- Extrathyroidal extension of cancer: a gross extrathyroidal invasion can be detected during a preoperative US scan (7). Kuo *et al.* (41) founded that detailed US assessment of extrathyroidal extension reliably ruled out microscopic invasion, reducing the rate of recurrence, improving preoperative risk stratification of patients and minimizing the rate of inadequate initial extent of surgery. Regarding the extrathyroidal extension, the last TNM classification (28) of thyroid cancer made significant changes in the definition of the T status. Indeed, while in the 7th edition of TNM classification (42), microscopic extrathyroidal extension of the tumor determined a T3 tumour, in the 8th TNM edition only tumors with gross extrathyroidal extension area classified as T3 (28).
- N status: if the lateral neck lymph nodes macroscopic involvement can be studied preoperatively (43), the role of preoperative US scan in detecting central neck lymph node metastases is still debated with a reported overall accuracy of 42–47% (44,45). Indeed, preoperative US can identify cervical lymph nodes involvement in 20–31% of cases (46,47). Zhang *et al.* (48) according to the last TNM classification evaluated the performance of preoperative US for staging, in a study on 665 PTC patients. The overall accuracy of preoperative US for N stage was 59%. The accuracy of US evaluation was respectively 81.8% for N0, 33.3% for N1a, and 87.5% for N1b. Zhao *et al.* (49) in a meta-analysis on 19 studies among 4,014 patients found that preoperative US reported poor sensitivity in the diagnosis of central lymph node metastases (33%) compared to the good diagnostic efficacy for lateral lymph node metastases (70%) in PTC patients.

Cytology molecular test

PTC is the most frequent histological type of differentiated thyroid cancer, followed by follicular thyroid carcinoma (31). It is nowadays possible to recognize high-risk features performing molecular tests with diagnostic (classification of a disease state), prognostic, or predictive purposes. Molecular tests were initially developed to reduce unnecessary diagnostic surgery in indeterminate thyroid nodules, but the real potentiality is to correctly define prognosis of thyroid malignancy. In this way, it would be possible to perform cytological molecular testing with the purpose of reduce overtreatment in patients with low-risk malignancy while performing adequate surgical treatment for those with higher risk. Authors agree that, for a correct risk stratification, it is necessary a correlation and comparison between clinical and molecular tests (50-52). Nikiforov *et al.* (53) performed a molecular analysis on 513 cytological indeterminate nodules samples, finding

87 positive results, of which 70% were *RAS* mutations. Although the overall risk of malignancy in a nodule negative for mutation was 14%, the overall risk of developing malignancy in a nodule with the presence of mutation was 89%. When the mutation testing was positive for *BRAF*, *RET-PTC*, or *PAX8-PPARγ*, the risk of malignancy was 100% (53).

Yip *et al.* (50) proposed an algorithm of molecular testing on cytological specimens, using a panel including *BRAF*, *RAS*, *PAX8-PPARγ*, and *RET-PTC*, demonstrating that association of cytology and molecular testing could lead to about 30% increasing of appropriate initial surgical treatment in PTC patients. However, some doubt still exists about the availability of the tests and the absence of level 1 evidences regarding their role in preoperative risk stratification (7,51).

Genetic investigations

It is known that specific genetic mutations are correlated with more aggressive behaviour of thyroid cancer (7). In particular, the correlation between *BRAF* mutation and PTC has been extensively studied; the presence of a *BRAFV600E* mutation is associated with lymph node metastasis in 65–77% of patients with PTC <1 cm (52,54,55). Moreover, in a meta-analysis including 2,470 PTC patients from 9 different countries, the *BRAFV600E* mutation was significantly associated with higher risk of recurrence (56). In addition, Xing *et al.* (54) report that specific molecular profiles in PTC patients (i.e., association of *BRAF* mutation with *TERT* promoter) are associated with worse prognosis when are expressed in combination: tumour recurrence rates were respectively 25.8% *vs.* 9.6% in *BRAF* mutation positive and negative patients, and respectively 47.5% *vs.* 11.4% in *TERT* mutation positive and negative patients. Patients harbouring both mutations had recurrence rates of 68.6% (56).

Surgical approach

Extent of thyroidectomy: TL vs. TT

TL guarantees residual thyroid function avoiding the risk of hypoparathyroidism and reducing the risk of laryngeal nerve palsy when compared to TT (7). On the other hand, if an aggressive PTC variant or incidentally detected central neck node metastases are documented at final histology, a completion thyroidectomy ± lymph node dissection is required in order to potentially allow radioactive iodine (RAI) treatment (14,20).

The last ATA guidelines (7) endorse TL as preferable surgical approach in unifocal, low risk T1–T2 PTC (7-9). Several authors reported no difference between TL and TT in terms of oncologic outcome in low-risk PTC patients (2,10,12,57,58).

Adam *et al.* (1), in a retrospective study among 61,775 PTC patients, reported no difference regarding overall survival for TL compared to TT in T1–T2 PTC patients and showed similar overall survival at 5, 10, and 14 years of follow-up (2). Kim *et al.* (57) published a 10-year-follow-up study comparing 1–5 cm cN0 PTC patients who underwent TL and TT. They found no significant difference between the two groups in terms of disease-free survival and recurrence rate. Furthermore, Kuba *et al.* (12) found no difference in terms of recurrence free survival and recurrence rate for patients with unilateral PTC 1–4 cm who underwent TL *vs.* TT on median 10 years follow-up.

Matsuzu *et al.* (10) in a retrospective study including 1,088 PTC patients who underwent TL plus central and/or lateral neck dissection, observed improved long-term oncologic outcome in younger patients (<45 years) showing tumors ≤40 mm, in absence of clinical lymph node metastases and extra-thyroidal invasion.

TT remains the initial surgical procedure of choice in PTC patients with high-risk features: tumor >4 cm, extrathyroidal extension and/or lymph node involvement, multifocality, previous neck irradiation, familial malignant thyroid disease (4,7).

However, most of the features that classified a PTC as intermediate-high risk, are postoperatively known. Indeed, several authors reported (16,59-61) a high prevalence of adverse pathological features (extrathyroidal extension, multifocality, and lymph nodes metastases) in PTC initially classified as low risk PTC in about 30–59% of patients (59,60).

Role of central neck nodal status

PTC patients with clinical evidence of central and/or lateral lymph node metastases (cN1) require TT plus central and/or lateral neck dissection as initial surgical treatment (7,62-64). Six (VI) level nodal dissection is mandatory in case of central neck node involvement and when mono- and/or bilateral therapeutic lateral neck dissection (including levels IIa-III-IV-Vb) is required (7).

The role of nodal status in PTC patients, plays a crucial

role in the prognostic evaluation of recurrence's risk (7). Podnos *et al.* (62) in a large cohort study of the SEER database showed that nodal involvement, age >45 years, large tumour size, and distant metastases, predicted a significantly poor overall survival. Moreover, the characteristics of central neck nodal involvement predict different risk of recurrence. Indeed, patients with clinical evidence of nodal metastases, larger size of nodal metastases, a multiple number of metastasized nodes and/or extranodal extension are at higher risk of recurrence when compared with those with microscopic nodal involvement (43,65-67).

If there is large agreement that lateral neck dissection must be performed only in clinical N1b patient (7), the role of prophylactic central neck lymph node dissection in cN0 PTC patients is still debated (68-73).

On the other hand, results of a meta-analysis (Liang *et al.*) (74), including 23 "high-quality" selected studies, found a rate of central neck node metastases ranging from 16.7% to 82.3% in patients underwent prophylactic central neck dissection. It's to note that this broad range is sufficient to demonstrate that is very difficult to obtain high quality of evidence recommendations. Probably the difference in expertise of preoperative US evaluation, surgical approach, and in the histological examination can explain the heterogeneous results in literature.

To date, there is no evidence supporting reliable preoperative parameters that allow to predict nodal disease in cN0 PTC (48,49,75).

The main arguments that favour a prophylactic central neck dissection are the improved accuracy of staging, a better selection for RAI treatment and the lowered levels of postoperative thyroglobulin, potentially leading to a reduction of the risk of recurrence (76,77).

Conversely, one of the main argument against is the higher risk of complications, namely hypoparathyroidism and laryngeal nerve injuries (69,78). In order to reduce the complications a more conservative (ipsilateral) central neck dissection (IpsiCND), including removal of pre-laryngeal, pre-tracheal and the para-tracheal lymph nodes homolateral to the side of the tumor, was proposed in patients with clinical unilateral PTC. Comparative studies have suggested that IpsiCND may be a valid alternative option to bilateral central neck dissection for cN0 PTC, considering similar short-term oncologic outcome and reduced risk of postoperative complications, in particular transient hypocalcemia (72,79,80). On the other hand, IpsiCND involves the risk of underestimate contralateral metastases (71). Since isolated contralateral metastases are uncommon (0–3.6%), it has been suggested that frozen section examination (FSE) on the ipsilateral central neck lymph nodes can be useful to assess intraoperatively the ipsilateral nodal status and consequently to modulate the extension of the prophylactic central neck dissection. Hartl *et al.* (45) found that FSE has a sensitivity, specificity and overall accuracy of 71.0%, 99.6%, 93.2% respectively in detecting lymph node metastases. In our experience, FSE had a sensitivity, specificity and overall accuracy of 80.7%, 100%, 90%, respectively, in detecting occult ipsilateral central neck metastases in clinically unifocal cN0 PTC (71-73). Most of the false negative results we observed were obtained in case of micrometastases, which are usually of little clinical significance (71-73).

Basing on our results, we supposed that this approach could allow to intraoperative identify clinically unifocal, intrathyroidal, cN0 PTC patients, initially scheduled for TL, with central neck nodal disease requiring TT and bilateral central neck dissection.

In a recent case-control study (personal series, unpublished data) we compared 30 clinically T1N0 PTC patients underwent TL + IpsiCND with FSE (TL-group) to a control group (C-group), matched by a propensity score analysis, who underwent TT + IpsiCND plus FSE. If FSE was positive for metastases, TT + bilateral central neck dissection was accomplished during the same procedure in the TL-group and bilateral central neck dissection in the C-group. Our results showed that IpsiCND-FSE allows for an accurate risk stratification of PTC patients eligible for TL. IpsiCND-FSE safely and correctly identify intraoperatively patients who benefit from TT + bilateral central neck dissection, reducing the need of a second-step completion procedure and, theoretically, the risk of recurrence.

Discussion

Current guidelines endorse TL as a valid surgical approach in case of low risk T1–T2 PTC (7-9).

Recent studies found no difference in overall survival between TL and TT in low risk PTC patients (1,10-13). However, up to one third of patients undergoing TL would require completion thyroidectomy because of aggressive histology (14-17,20). The implementation of updated ATA and NCCN guidelines and the American Joint Committee on Cancer (AJCC) staging system would likely drop this subgroup to 11%. Locoregional recurrence following TL were reported under 6% and managed with completion

thyroidectomy (7-9,27).

Of note tumor size alone is not a reliable indicator of PTC aggressiveness, since microPTC (≤1 cm) may present also distant metastases and macroPTC may be totally indolent all life long after initial surgery (20-22).

Previous neck irradiation, familial history of PTC, extrathyroidal extension, central and/or lateral lymph node metastases remain high-risk features requiring at least TT as initial surgical approach (7,10). Furthermore, there are some high-risk features that became evident only after final histology such as aggressive variants of PTC, extracapsular invasion, vascular invasion, occult nodal metastases, extranodal extension. These features suggest in many cases completion thyroidectomy and radioiodine treatment or intensive follow-up (7-9,23).

An accurate preoperative risk stratification is mandatory to individualize the best initial surgical approach to PTC. Clinical history, pre-operative US, cytologic evaluation allow a first risk stratification, while molecular and genetic studies are still investigational and not anywhere applicable (7,10,25,26,50-52).

In spite of these considerations, occult nodal disease occur in up to 50–80% of patients and is not always microscopic nodal disease (7,67,80). To date there are no evidence to suggest unequivocal pre-operatively available clinical parameter as reliable predictor of nodal disease in cN0 PTC (42,43,46,47,75).

IpsiCND FSE has been validated to intraoperatively assess the nodal status in cN0 low risk patients in which a prophylactic central neck dissection is not mandatory in order to intraoperatively modulate the extension of nodal dissection (81).

Considering the high accuracy of FSE of the ipsilateral central neck nodes in defining the nodal status cN0 PTC patients (up to 90%), we postulated that FSE of IpsiCND could be useful to modulate the extension of surgical resection in those PTC patients eligible for TL (62-64). Indeed, if occult ipsilateral central neck node metastases occur, TT and central compartment dissection become mandatory (7-9,82). To date we adopted such surgical approach to personalize the extension of the surgical resection in small (T1), unifocal, cN0 PTC, eligible for TL in a case-control study including 60 patients (unpublished data) aiming to evaluate the results of such approach for personalizing the management of PTC patients initially scheduled for TL. We found that IpsiCND-FSE can safely and correctly identify during the operation patients who benefit from TT plus bilateral central neck dissection, reducing the need of a second-step completion procedure and, theoretically, the risk of recurrence.

Extent of thyroidectomy for low risk PTC is still debated. In spite of these controversies pN1 status is still considered a high-risk characteristic requiring a surgical strategy more than a TL. In our series all the patients, initially scheduled TL, with occult macro N1a disease were detected intraoperatively after FSE on IpsiCND and the completion thyroidectomy and central neck dissection were performed during the same operation. Larger prospective studies are necessary to further validate our findings but the results seem encouraging especially when dealing with a conservative surgical approach for oncologic disease reliably excluding more advanced disease which could benefit from a more aggressive initial operation. Indeed, PTC recurrences implied a reduced quality of life and often a technical demanding surgical re-exploration (17). From this point of view the choice of initial surgical treatment became of utmost importance and it is mandatory not using tumor size alone to modulate the operative approach (20). Of note, in some retrospective series the prevalence of adverse pathological features in initial low risk PTC have been reported: 30–59% of patients may be upstaged to a higher risk category after undergoing TL (59-61).

Although guidelines have evolved to allow for less aggressive treatment options [active surveillance or TL without the need for RAI or thyroid stimulating hormone (TSH) suppressive therapy] these recommendations are only applicable to properly selected patients. In other words, to date, despite guidelines recommendations, the best initial extent of thyroidectomy for low risk PTC is still debated. In spite of these controversies pN1 status is still considered a high-risk characteristic requiring a surgical strategy more than a TL. In our series all the patients, initially scheduled TL, with occult macro N1a disease were detected intraoperatively after FSE on IpsiCND and the completion thyroidectomy and central neck dissection were performed during the same operation. Larger prospective studies are necessary to further validate our findings but the results seem encouraging especially when dealing with a conservative surgical approach for oncologic disease reliably excluding more advanced disease which could benefit from a more aggressive initial operation.

Conclusions

TL should be safely accomplished basing on available evidence in case of intrathyroidal N0 PTC, if the nodal

status is reliable proven. In this setting the role of N staging is at our knowledge underestimated since many patients after TL are Nx patients and no N0 patients. Moreover, the occult central nodal disease is not always microscopic and negligible. Strong evidences for accurate preoperative risk stratification are needed and probably molecular tests on cytologic samples can provide further information regarding tumor aggressiveness in order to reliably modulate the extent of initial surgery for PTC.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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