PATHOLOGICA 2025;117:111-120;
DOI: 10.32074/1591-951X-1091

Original article

Evaluation of papillary thryoid carcinoma and its variants: multifocality in thyroid lobectomy and completion thyroidectomy - a single tertiary center retrospective study

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Summary

Aims. The American Thyroid Association (ATA) updated guidelines for the treatment of thyroid cancer, leading to a less aggressive approach depending on clinical-pathological features. As a result, the possibility to perform lobectomy versus total thyroidectomy has significantly increased. The majority of thyroid cancers are indolent with an excellent prognosis, while only 15% of patients with well-differentiated carcinoma, including papillary thyroid carcinoma (PTC), have locally advanced thyroid cancer (LATC) at diagnosis. We reviewed our practice in treating thyroid carcinoma over the last decade.

Methods. From January 2010 to December 2020, 1057 patients with uninodular benign and malignant thyroid lesions were reviewed.

Results. Among these cases, 77% were women with a median age of 49.3 years. The series involved 307 malignant diagnoses (29.05%) including 196 (61.6%) classic PTC and 38 (12%) aggressive variants of PTC, mostly tall cell variant (30 cases, 9.4%). Among malignant cases, multifocality was microscopically documented in 84 cases (26.4%). Using the ATA distribution of risk, there were 239 cases in the low risk and 68 in the intermediate risk categories. Second surgery was assessed in a total of 150 cases, showing 42 cases with additional thyroid cancer foci in the other lobe (26 single vs 16 multiple foci). Ten cases had metastatic perithyroidal lymph nodes.

Conclusion. Our data could be the basis for performing a longitudinal study in order to establish which risk factors can predict bilateral involvement and to suggest a tailored surgical approach.

Key words: fine needle aspiration cytology, thyroid cancer, lobectomy, total thyroidectomy, personalized medicine

Received: September 14, 2024
Accepted: January 8, 2025

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How to cite this article: Bruno C, Tralongo P, Vegni F, et al. Evaluation of Papillary thryoid carcinoma and its variants: multifocality in thyroid lobectomy and completion thyroidectomy - a single tertiary center retrospective study. Pathologica 2025;117:111-120. https://doi.org/10.32074/1591-951X-1091

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Introduction

In recent decades we have witnessed an increased incidence of thyroid cancers [1-3]. Nonetheless, despite the increase of new thyroid cancers, the number of related deaths has remained stable [3-4]. These data confirm that the biologic behavior of most thyroid malignancies is associated with an excellent survival rate, with only a minority characterized by recurrences and local or distant metastases [1-4]. This is especially true for low risk differentiated thyroid cancers, leading to the fact that some international guidelines have suggested active surveillance, conservative

surgery, and a raised threshold for radioactive iodine ablation (RAIA) [4-6].

In 2015, the American Thyroid Association (ATA) proposed that lobectomy should be used in the treatment of low risk differentiated thyroid cancers [4]. For this reason, the extent of surgery, especially for well-differentiated thyroid cancers that are defined by low-risk stage as well as unifocal and intrathyroidal disease without lymph node metastases, has been debated for several years [7-17]. Typically, the surgical approach for thyroid cancer is total thyroidectomy in cancers greater than 1 cm. Nevertheless, several recent studies have not confirmed a definitive association between extent of surgery and survival rate, suggesting that low-risk single thyroid cancers such as those smaller than 4 cm, are likely to benefit from unilateral treatment such as lobectomy.

Similarly, guidelines from other associations such as the British Thyroid Association for the management of thyroid cancer and the Italian Consensus guideline for the diagnosis and treatment of differentiated thyroid cancer have also suggested lobectomy for some types of thyroid cancers [5-6]. The suggestions to adopt a more conservative surgical approach in the treatment of selected cases of thyroid malignancies such as PTC were mostly based on results obtained from large population studies confirming that for low-risk thyroid malignancies, total thyroidectomy and lobectomy yielded similar results in terms of overall patient survival. The selected cases have specific criteria such as: age < 45 years, tumor size ≤40 mm, no clinical lymph node metastases, and no extra-thyroidal invasion [5]. On the other hand, in the recent version of the ATA guidelines [4], total thyroidectomy was the leading approach proposed for tumors > 4 or < 4 cm with high-risk features including family history of thyroid carcinoma, prior neck irradiation, multifocality, extrathyroidal extension and central and/or lateral lymph node neck involvement.

Several retrospective and prospective series reported no differences regarding overall survival for lobectomy compared to total thyroidectomy in T1-T2 PTC at 5, 10, and 14 years of follow-up [18-19]. For proper patient selection to guide management, correct stratification of preoperative risks, relying on ultrasound evaluation and fine needle aspiration cytology (FNAC), is necessary to tailor surgical management [20]. However, the majority of relevant prognostic factors for risk stratification of PTC patients are often not preoperatively available and only available from the histological report after resection, including the presence of microscopic multifocality and/or extra-thyroidal extension, central neck nodal status, aggressive histological variant, etc. [7-9,23,24]. Once such histological parameters are known, postoperative upstaging to a higher-risk category may occur in up of 40% of cases initially treated with lobectomy.

In the current paper, we analyze our experience and the features justifying a lobectomy and then a second surgery required based on a histological diagnosis.

Materials and methods

A retrospective search was performed for all thyroid gland lobectomies performed over a 10-year period (January 2010 to December 2020) at the Fondazione Policlinico Universitario "Agostino Gemelli" in Rome, Italy. The institution's electronic medical record system Armonia-Metafora, Italy (CU) was searched for thyroidectomy and thyroid lobectomy specimens during the study period. Patient age, gender, FNAC diagnoses, and follow-up surgical pathology information were recorded. All available pathology slides were reviewed (including cytological and histological samples). For cytological interpretation, all the thyroid nodules were evaluated and biopsied under ultrasound guidance by clinicians and radiologists. We received internal institutional ethical approval for this study (I.N. 14322).

All malignant cases had a previous FNAC [20-22] processed using a ThinPrep 5000TM processor (Hologic Co., Marlborough, MA, USA). The cytological cases were classified and diagnosed according to the new Italian Working Group SIAPEC-IAP classification [22]. All the cases were re-evaluated and then re-classified according to The Bethesda System for Reporting Thyroid Cytology II (TBSRTC, 2017) [20]. For malignant cases or those with suspicion of malignancy, an ultrasound (US) evaluation of VI level lymph nodes was performed and an FNAC also performed in cases in which the US criteria were suggestive for a possible metastatic localization. We performed immunocytochemical staining for VE1-BRAF on LBC stored material according to our standard protocol as described in different papers [23-25].

Histopathology specimens

All surgical pathology specimens were fixed in 10% buffered formaldehyde, embedded in paraffin, sectioned into 5 micron-thick slides and then stained with hematoxylin-eosin (H&E). The diagnosis of classical variant/subtype of papillary thyroid carcinoma (c-PTC), different PTC variants/subtypes, poorly differentiated thyroid carcinoma (PDTC), medullary thyroid carcinoma (MTC) and anaplastic thyroid carcinoma (ATC) were classified according to the 2017 WHO Classification of Tumors of Endocrine Organs [26]. For the definition of tall cell variant/subtype (TCV) of

PTC, we included cases of PTC with equal or more than 30% TCV component. The histological diagnosis of non-invasive follicular thyroid neoplasm with papillary like nuclear features (NIFTP) was rendered according to the criteria described by Nikiforov et al. [27]. All malignant cases were staged according to the 8th edition of the tumor-node-metastasis (TNM)-based staging system recommended by the American Joint Commission on Cancer (AJCC) [25]. The follow-up period ranged from 2 to 120 months (median 59 months; mean 57.9 months). The histological cases were also classified according to the ATA risk categories, as described in the result session [4].

Statistical analysis

Statistical analysis was performed using GraphPad-Prism 6 software (Graph Pad Software, San Diego, CA) and PSPP version 1.4.1 (GNU Project, Free Software Foundation, Boston, MA). Comparison of categorical variables was performed using the chi-square statistic and the Fisher's exact test. P-values less than 0.05 were considered as statistically significant.

Results

Our study included 1057 histological cases treated with thyroid lobectomy, including 739 (69%) benign, 11 (1.05%) NIFTP and 307 (29.05%) malignant diagnoses. Patient demographics and clinical-pathological features are described in Table I. The series included 243 male (23%) and 814 female (77%) patients with a mean age of 49.32 years (median 49.50 ys; IQR 40.50). The mean size of thyroid nodules was 1.4 cm, ranging in size from 0.1 to 5 cm (Tab. I), with a median dimension of 1.25 cm (IQR 2.42). In the malignant cases, 150 (47.2%) underwent a second surgery on the other lobe. Among the 739 benign lesions removed with a lobectomy due to compressive symptoms and size, the final histological diagnoses included 226 follicular adenomas (FA), adenomatous nodules in 507 cases, and one case with Hashimoto thyroiditis. None of these cases underwent a second surgery (data were not tabulated for benign lesions). Of note, the majority of benign lesions had a size between 1.7 and 5 cm, leading to surgery for aesthetic reasons and compressive symptoms. In 48 cases out of 739 benign lesions, we found single foci of PTC smaller than 4 mm (median size 1.80 mm; IQR 2.05). None of these cases had a multifocal PTC. None of them had contro-lateral lobectomy. Furthermore, our series also included 11 cases diagnosed as NIFTP. The malignant cases underwent lobectomy based on the small size of the lesions and the evidence of a single nodule previously observed with US evaluation. Analyzing the clinical-pathological data, including age, size, and the other parameters described in Table I we found no statistical significance for any parameter. Table II shows the distribution of the cases, including 11 NIFTP and 307 cases with malignant histopathological diagnoses. This latter group included 196 cases of classical PTC (Fig. 1), 42 invasive follicular variants of papillary thyroid carcinoma (I-FVPTC), 30 "tall-cell" variant cases, 6 hobnail subtypes of PTC, 2 solid subtypes of PTC, 4 columnar cell subtypes of PTC (CC-PTC), 9 Warthin-like subtypes, 15 follicular thyroid carcinoma (FTC) cases, 2 PDTC cases, and 1 MTC (size 0.5 cm) (Tab. II). Thus, it is clear that the majority of the malignant population is composed of classic PTC and its subtypes. The data are mostly focused on that PTC group, especially because none of the FTC, PDTC and MTC showed multifocality and/or lymph node involvement,

Table I. Summary of clinical-pathologic data.

Clinical-pathological features	Proportion (n = 1057)
Age	
Mean	49.32 years
Median	49.50 years
IQR	40.5
Gender	
Male	243 (35%)
Female	814 (65%)
Histopathological diagnosis	
Benign	739 (69%)
NIFTP	11 (1%)
Malignant	307 (29%) ç
Cytological diagnosis (n = 318) *	
Non-Diagnostic	0 (0%)
Benign	0 (0%)
AUS/FLUS	0 (0%)
FN/SFN	18ç (5.7%)
SFM	15ç (4.7%)
Malignant	285 (89.6%)
Lymph node involvement §	
Positive Central VI level	51 (24%)
Lateral cervical involvement	5 (2.4%)
Completion surgery°	150 (47.2%)
Multifocality	
Same lobe	84 (26.4%)
Opposite lobe	42 (28%)

Legend: AUS/FLUS: Atypia of Undetermined Significance/Follicular Lesion of Undetermined Significance; FN/SFN: Follicular Neoplasm; NIFTP: non-invasive follicular thyroid neoplasm with papillary like nuclear features; SFM: suspicious for malignancy;

* FNAC diagnoses on the 318 malignant cases; ç including 11 NIFTP as 5 FN and 6 SFM; °performed on the malignant group of 318 malignancies; § 212 cases with central VI level removal.

Table II. Histological diagnoses and morphological features.

Histological diagnoses	Number of cases	Multifocality	Lymph node involvement§
NIFTP	11 (3.5%)	0 (0%)	0 (0%)
Classical PTC	196 (61.6%)	66 (20.8%)	10 (3.1%) [8 micromets (2.5%); 2 macromets (0.6%)]
I-FVPTC	42 (13.2%)	10 (3.1%)	0 (0%)
TCV	30 (9.4%)	7 (2.2%)	38 (11.9%) [20 micromets (6.3%); 18 macromets (5.7%)]
CC-PTC	4 (1.3%)	0 (0%)	0 (0%)
Hobnail PTC	6 (1.9%)	1 (0.3%)	3 macromets (0.9%)
Solid subtype PTC	2 (0.6%)	0 (0%)	0 (0%)
Warthin-like PTC subtype	9 (2.8%)	0 (0%)	0 (0%)
FTC	15 (4.7%)	0 (0%)	0 (0%)
MTC	1 (0.3%)	0 (0%)	0 (0%)
PDTC	2 (0.6%)	0 (0%)	0 (0%)

Legend: NIFTP: Non-invasive follicular thyroid neoplasm with papillary-like nuclear features; c-PTC: classic Papillary thyroid carcinoma, I-FVPTC: invasive follicular variant of PTC, TCV: Tall Cell variant of PTC; FTC: Follicular thyroidcarcinoma; CC-PTC: Columnar cell variant of PTC, PDTC: poorly differentiated thyroid carcinoma, MTC: medullary thyroid carcinoma; § 212 lymph nodal dissection.

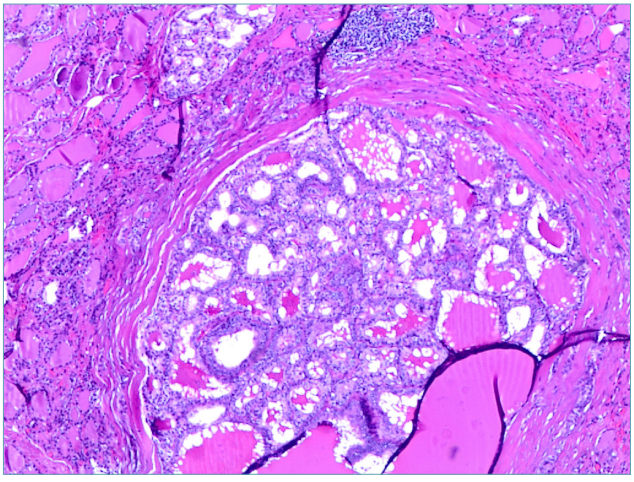

Figure 1. Histological findings of a case with millimeter-sized PTCs (100x H&E). This case was uncapsulated with the typical features of PTC, concerning nuclei and cellular architecture. The patient had a previous FNAC diagnosed as malignant. The patient had a second surgery due to millimeter PTCs as seen in Figure 2. The follow-up was disease free.

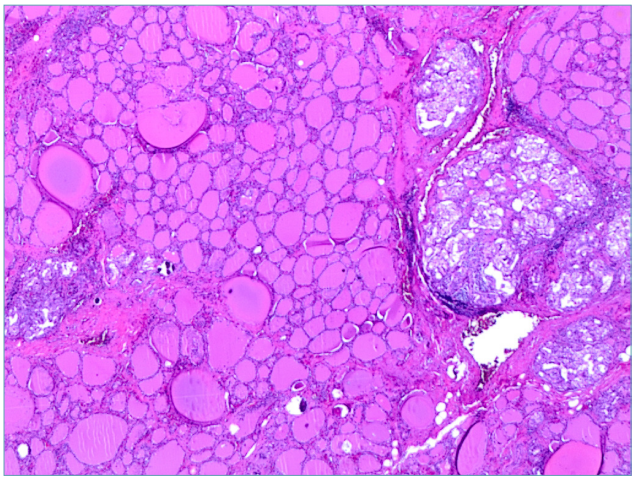

Figure 2. Histological features of additional neoplastic foci of PTC from the case in picture 1 (200X, H&E).

Eighty-four cases out of 307 (27.3%) had microscopic multifocality in the same lobe (Fig. 2). The multifocality was distributed as follows: 66 c-PTC, 7 TCV, 10 I-FVPTC, and 1 hobnail subtype of PTC. The foci of thyroid carcinoma ranged from one to four additional carcinomatous foci with a size comprised between 3 mm and 7 mm. Among the malignant group, lobectomy included ipsilateral VI level lymph node dissection in 212 cases (69%), which was performed due to the previous positive lymph node FNACs (24 cases) and also the macroscopic evidence of surgically suspected lymph nodes during the surgery (188 cases), for which an intrasurgical evaluation was requested by the surgeons. To note, 51 cases out of 212 (24%) showed a positive ipsilateral VI level involvement (N1a) which was confirmed during the intraoperative examination performed in cases with suspicious and enlarged lymph nodes. There were 28 lymph nodes that showed micrometastases and 23 macrometastases. None of the lymph nodes had extranodal involvement. Combining the ATA classes of risk stratification, the first lobectomy showed that 239 cases were ATA low risk, then 68 cases belonged to the intermediate risk category, due to aggressive histotypes (45 cases), lymph node metastases (23 cases), vascular and or capsular invasion (20 cases included in the group of 45 cases with aggressive histotypes), justifying the completion. Specifically, among the 239 low risk cases, only 28 cases had lymph node micrometastases in less than 5 lymph nodes (ranging from 2 to 5 lymph nodes). For the intermediate ATA risk, 23 cases had a macrometastasis in at least 5 lymph nodes, with a size smaller than 3 cm.

The 23 cases with macrometastatic lymph nodes underwent completion surgery during the first surgical procedure, as well as a lateral cervical neck dissection (level II to V). Of these, five cases showed additional macrometastases. Of note, the 28 micrometastases were found in 20 TCV cases and 8 c-PTC cases, while the 23 cases with macrometastases were detected in two c-PTC cases, 18 TCV cases and 3 hobnail PTC cases. We found 23 additional cases with micro- (Fig. 3) and/or macrometastases in the VI level lymph nodes, with only 2 cases with extranodal involvement. In Table III we highlight the cytological-histological correlation for the 318 cases that underwent preoperative FNAC, including 307 malignancies and 11 NIFTP. All of the malignant histological cases underwent a previous FNAC with a diagnosis rendered belonging to one of the following categories: 285 malignant, 15 SFM and 18 FN. The 11 NIFTP had been diagnosed as 6 SFM and 5 FN. All the malignant and SFM cases were also evaluated for US analysis of VI level lymph nodes, leading to a cytological evaluation in 57 of them, with 24 positive metastatic diagnoses. According to our cytologic protocol, we perform on LBC stored material the immunocytochemical evaluation for VE1-BRAF. Specifically we founo colon only 10 cases positive for VE1-BRAF, all diagnosed as Malignant category, whilst all the other were negative for VE1-BRAF. Among these 10 BRAF positive cases, 5 also had positive VI level lymph nodes and all belonged to the Tall cell subtype.

Table IV shows the distribution for 150 cases with completion thyroidectomy out of the 307 malignant cases. None of the 11 NIFTP had a completion, justified by the definition of this entity. In the other lobe, we

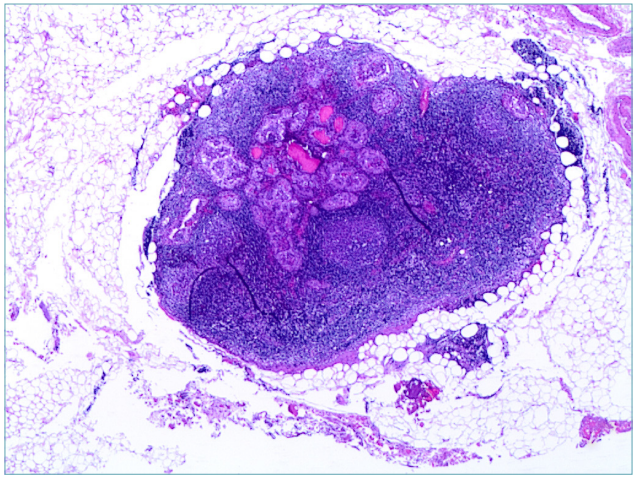

Figure 3. Evidence of lymph node metastasis in a case of completion thyroidectomy (200x H&E).

Table IV. Histological findings in 150 completion thyroidectomies.

Histological diagnoses	Multifocality	Lymph node involvement after second surgery
NIFTP	0 (0%)	0 (0%)
c-PTC	30 (20%)	10 (6.7%)
I-FVPTC	4 (2.7%)	0 (0%)
TCV	7 (4.7%)	0 (0%)
CC-PTC	0 (0%)	0 (0%)
Hobnail PTC	0 (0%)	0 (0%)
Solid subtype PTC	0 (0%)	0 (0%)
Warthin-like PTC subtype	0 (0%)	0 (0%)
FTC	0 (0%)	0 (0%)
MTC	1 (0.7%)	0 (0%)
PDTC	0 (0%)	0 (0%)

Legend: NIFTP: Non-invasive follicular thyroid neoplasm with papillary-like nuclear features; c-PTC: classic Papillary thyroid carcinoma, I-FVPTC: invasive follicular variant of PTC, TCV: Tall Cell variant of PTC; FTC: Follicular thyroidcarcinoma; CC-PTC: Columnar cell variant of PTC, PDTC: poorly differentiated thyroid carcinoma, MTC: medullary thyroid carcinoma.

Table III. Cyto-histological correlation.

Diagnoses*	c-PTC	I-FVPTC	TCV	SOLID PTC	HOBNAIL-PTC	CC-PTC	Warthin-PTC	MTC	FTC	PDTC	NIFTP
PM	194 (61%)	41 (12.9%)	28 (8.8%)	2 (0.6%)	6 (1.9%)	4 (1.3%)	9 (2.8%)	1 (0.3%)	0 (0%)	0 (0%)	0 (0%)
SFM	2 (0.6%)	1 (0.3%)	2 (0.6%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0.3%)	9 (2.8%)
SFN/FN	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	15 (4.7%)	1 (0.3%)	2 (0.6%)

Legend: AUS/FLUS: Atypia of Undetermined Significance/Follicular Lesion of Undetermined Significance; FN/SFN: Follicular Neoplasm/Suspicious for Follicular Neoplasm; SFM: Suspicious for Malignancy; c-PTC: classic Papillary thyroid carcinoma, I-FVPTC: invasive follicular variant of PTC, FTC: Follicular thyroidcarcinoma; CC-PTC: Columnar cell variant of PTC, PDTC: Poorly differentiated thyroid carcinoma, MTC: medullary thyroid carcinoma; NIFTP: Non-invasive follicular thyroid neoplasm with papillary-like nuclear features

*none of our cases has been diagnosed as AUS/FLUS or Benign

found 42 cases with additional foci of carcinoma and 108 that were negative for additional neoplastic foci. The 42 cases included 30 cases of c-PTC, 4 I-FVPTC cases, 7 TCV cases and 1 MTC (Tab. II). These 42 cases with thyroid cancer in the other lobe showed 26 single foci and 16 multiple additional foci. Specifically, the 16 multifocal cancers were in the number between 1 and 5 additional foci with a 1-5 mm size. In seven cases from the c-PTC group, we found additional lymph node metastases. Furthermore, in three cases we found only additional lymph node metastases without any parenchymal malignant foci. The reason leading to a completion thyroidectomy were represented by: multifocality in the same lobe (84 cases); positive lymph nodes (51 cases) and 15 cases showing histological features of aggressive subtypes (mostly PTC subtypes) and a peripheral location of the neoplasm infiltrating microscopically the inked margins.

Tumor stage data revealed that there were 298 stage I cases, 5 stage II cases, 2 stage III cases, 2 IVa cases, and 0 stage IVb cases. The majority of cases belonged to stage I, with 7 of the aggressive variants of PTC (including TCV, CC-PTC and hobnail subtypes) classified as stage II or III. One TCV and one MTC cases were classified as stage IV. We also performed a chi-square test, evaluating the association between tumor histotype and staging according to the AJCC TNM 8th edition (2016), which yielded a p value of 0.13, thus showing a statistically significant association of more aggressive tumor histotypes with higher tumor stages.

We also evaluated the association of disease-free survival (DFS) and overall survival (OS) with lymph node metastases. The follow-up period ranged from 2 to 120 months. Considering the different lymph node stations and DFS, we did not find any significant correlations. None of our patients died of thyroid disease and/or had any distant metastases or late recurrences. In the series with second surgery we reported 25 local recurrences as lymph nodes (10 cases) and nodular areas in the perithyroid site (15 cases). For the group that did not have a second surgery, we found only 8

Table V. Summary of the main features of ultrasound-based thyroid nodule systems.

ACR-TIRADS	Korean system	UK BTA system
cystic = 0 spongiform = 0 mixed solid and cystic = 1 solid = 2	K-TIRADS 1: no nodule	U 1: No nodule
anechoic = 0 hyperechoic or isoechoic = 1 hypoechoic = 2 very hypoechoic = 3	K-TIRADS 2: Benign	U 2: Benign hyperechoic or isoechoic with a halo cystic change with ring-down artifact (colloid) microcystic or spongiform appearance peripheral egg-shell calcification peripheral vascularity
wider-than-tall = 0 taller-than-wide = 3	K-TIRADS 3: Low partially cystic / isohyperechoic with no suspicious features	U3: Indeterminate solid homogenous markedly hyperechoic nodule with halo (follicular lesions) hypoechoic with equivocal echogenic foci or cystic change mixed or central vascularity
smooth = 0 ill-defined = 0 lobulated or irregular = 2 extrathyroid extension = 3	K-TIRADS 4: Intermediate as for K-TIRADS 3 but with any suspicious features or as for K-TIRADS 5 without suspicious features	U4: Suspicious solid hypoechoic (compared with thyroid) solid very hypoechoic (compared with strap muscles) hypoechoic with disrupted peripheral calcification lobulated outline
none or large comet-tail artifacts = 0 macrocalcifications = 1 peripheral calcifications = 2 punctate echogenic foci = 3	K-TIRADS 5: High solid hypoechoic nodule with any suspicious feature	U5 Malignant solid hypoechoic with a lobulated or irregular outline and microcalcification papillary carcinoma solid hypoechoic with a lobulated or irregular outline and globular calcification medullary carcinoma intranodular vascularity taller than wide axially (AP > ML) characteristic associated lymphadenopathy

Table VI. TIRADS categories (sum of all the points) for thyroid nodules.

Categories	TR1	TR2	TR3	TR4	TR5
Points	0	2	3	TR4a = 4 TR4b = 5 TR4c = 6	> 7
Features	Benign	Not suspicious	Mildly suspicious	Moderately suspicious	Highly suspicious

recurrences as 5 lymph nodes and 3 nodular areas in the perithyroid site. In the latter group, US follow-up of the other lobe together with the evaluation of thyroid blood exams, did not show any suspect nodular area. In both groups, the lesions were diagnosed with a FNAC and then confirmed with histological evaluation, in a range between 3 and 15 months (mean 6.7 months). We also compared DFS and OS with the group of patients who did not have a second lobectomy and found no statistically significant differences, demonstrating that even in cases of multifocality, and lymph node localization, the majority of PTC and its subtypes are indolent.

Table V and VI show the criteria and score adopted for the evaluation of thyroid nodules resulting helpful for the evaluation of the most appropriate clinical and/or surgical procedure. All the cases that underwent surgery had a high TIRADs score, between 5 and > 7, which was also combined with the cytological diagnosis. Specifically, they were all hypoechoic, ill-defined, with 43 cases showing taller than wider pattern, and peripheral calcifications.

Discussion

The current paper deals with the evaluation of lobectomy for the treatment of thyroid malignancy, composed mostly of cases with well-differentiated tumors, especially classic PTC and its subtypes. In our series we aimed to analyze the features that led to completion of thyroid gland surgery and the possible lesions encountered in the other lobe justifying a second surgery.

The incidence of PTC and thyroid microcarcinomas has increased in recent decades [1-3]. The main reason is related to the detailed pre-operative evaluation of thyroid nodules nowadays being undertaken with ultrasound (US) and FNAC. These procedures are able to detect even small malignant nodules to be analyzed and evaluated [28-30]. Despite the increasing number of cases, most well-differentiated thyroid cancers, and especially classic PTC, show a very indolent outcome with a survival rate of up to 90% after 10 years [31-33]. A long debate has been going on, discussing the best surgical approach and if lobectomy can be a valid and optimal substitute to a total thyroidectomy.

Several studies have evaluated recurrence-free survival following total thyroidectomy versus lobectomy to define the best surgical approach [7-17]. For, instance, Van Gerwen et al. analyzed 1117 studies confirming that micro PTC cases exhibit an excellent long-term recurrence-free survival with both total thyroidectomy and lobectomy [7,34]. These results are extremely useful to limit the possible risk factors and post-surgical complications which may affect total thyroidectomy. Nonetheless, the decision about which specific surgical management is no comma is mostly determined by the pre-operative evaluation of thyroid nodules, including US and FNAC not only about the thyroid nodules but also analyzing VI level for lymph nodes. Specifically, Tables V and VI show the US criteria and scores that are helpful for the appropriateness of surgery and that have been largely analyzed in many studies [35-36].

Current guidelines suggest lobectomy for thyroid indeterminate diagnoses such as AUS/FLUS and FN, but also for SFM and malignant lesions [4]. Even if the adoption of lobectomy for indeterminate lesions is the gold standard, its role following a cytological diagnosis of malignancy remains controversial showing significant differences in the surgical approach, all over the world [1-10]. In fact, the decision to perform a lobectomy is mostly associated with a primary tumor < 4 cm and where there is no extrathyroidal extension or lymph node metastases. Despite the fact that these parameters are likely to be considered the most relevant in the defintion of the best surgical procedure, the authors want to underline that some further important clinico-pathological risk factors, including microscopic extrathyroidal extension, aggressive histology, multifocal cancer, vascular invasion in PTC and nodal metastases, can only be identified after completing a thyroid lobectomy. It is still controversial whether and when patients with these additional histological risk factors should undergo complete thyroidectomy and/or radioactive iodine remnant ablation or be monitored without any further treatment. This is also based on evidence that the recurrence rate in lobectomies is low and that if recurrences can be easily detected with US and subsequent surgery undertaken without any

impact on life [7-15].

The 2015 ATA guidelines established that lobectomy is the appropriate conservative treatment for low risk well-differentiated thyroid cancers, especially for patients with mild thyroid-stimulating hormone (TSH) level suppression (0.5-2 mU/L). Nonetheless, the optimal extent of surgery remains controversial [4]. DiMarco et al. studied 275 patients who met ATA criteria for lobectomy, showing concordance in only 57% of them. The remaining 43% showed discrepancies related to angioinvasion, local invasion, or both leading to completion thyroidectomy [13].

Hence, we analyzed lobectomies with a diagnosis of malignancy (mostly represented by PTC and its subtypes) and the detection of histological high-grade risk parameters that led to completion surgery in half of them. According to the ATA classes of risk stratification, 239 were ATA low risk and 68 cases of our series belonged to the intermediate risk group, suggesting the completion.

An immediate conversion was performed in 23 cases with lymph node macrometastases detected during the intraoperative examination. It is interesting to note that histological findings documented the evidence of additional multiple foci of cancer in 16 cases (69.5%). This evidence was rarely linked to a lobectomy with a single PTC without additional aggressive parameters. The additional malignant foci had a tumor size ranging between 1 mm and 5 mm.

It is important to emphasize that an accurate pre-surgical analysis performed by experienced US physicians and cytopathologists is likely to foresee and suggest the most appropriate surgical approach, which is mostly defined by a lobectomy in the presence of a single lesion, circumscribed, without extra thyroidal invasion. Craig et al. studied intraoperative assessment for lobectomy, showing that 74% of their patients were eligible for initial lobectomy, with 21% showing high risk factors highlighted during intraoperative examination which induced a conversion to a total thyroidectomy [14]. These authors also underlined the role of intraoperative management in selected cases with suspicion for high-risk factors, even though up to 30% of their patients needed a completion thyroidectomy [14]. In our series, 23 cases (7.5%) underwent a conversion after a lobectomy. In our institution we perform an US FNAC on the VI level lymph nodes in high risk cases and also macroscopic evaluation with frozen session, in cases with suspicion. This evidence is mostly due to the fact that at our institution, during lobectomy we perform an intraoperative examination only in cases with macroscopically suspicious lymph nodes of the central neck district. The remaining 127 completion thyroidectomies in our series were attributed to a second surgery after a histological diagnosis was rendered.

Furthermore, we also performed lobectomy plus ipsilateral VI level lymph node dissection in 212 cases (69%), which was performed due to the previous cytological diagnosis of metastatic lymph nodes and also the macroscopic evidence of surgically suspected lymph nodes. The remaining 31% had a negative presurgical cytological evaluation of lymph nodes, without any intraoperative evaluation and/or surgical removal. Kluijfhout et al. evaluated how often a completion thyroidectomy would have been necessary if the initial lobectomy was performed in patients with 1-4 cm well-differentiated thyroid cancer without preoperatively known risk factors [15]. In their retrospective analysis, they demonstrated that half of their 287 patients eligible for lobectomy would have benefited from a completion, including 0.5% of the cases with TCV, 34% of the cases with angioinvasion, 18% of the cases with positive margins, 17% of the cases with extrathyroidal extension, and 18% of the cases with lymph node metastases (15). In our series, the criteria adopted in the 138 completion surgeries included 23 cases (7.5%) with lymph node metastases, 33 cases (10.7%) with aggressive cancers (including PTC and its subtypes, MTC, PDTC), 35 cases (11.4%) with angioinvasion, and 15 cases (4.9%) with extrathyroidal extension.

Different authors have discussed the comparative role of lobectomy versus total thyroidectomy [7-17]. Matsuzu et al. analyzed a series of 1088 PTC patients who underwent lobectomy and concluded that the long-term clinical outcome was excellent, especially for patients younger than 45 years, whose tumor was 4 cm or less, and in patients without any positive lymph node or extrathyroidal tumor [10]. Liu et al., in their series of 4320 PTC cases (including 1087 intermediate-risk PTC cases according to the ATA guidelines), confirmed that recurrence-free survival and disease specific survival were similar for lobectomy and total thyroidectomy, but without statistical significance ($p = 0.622$ and $p = 0.554$) [11]. Macedo et al. performed a meta-analysis focused on different thyroid surgery options, including total thyroidectomy and lobectomy [16]. Their evaluation was performed on 6 studies including 2939 patients distributed as 72.6% total thyroidectomies and 27.4% lobectomies. They found a lower recurrence rate for total thyroidectomy (4.4%) versus lobectomy (8.8%), mostly attributable to a more complete dissection of the central nodal compartment at the time of initial surgery. Of note, in our series we have not compared lobectomy to total thyroidectomy because our first focus was to evaluate the parameters and criteria helpful in the management of lobectomy and eventual completion surgery. According to our results, the main

reasons for a completion of surgery is associated to the detection of multiple neoplastic foci in the lobectomy, followed by lymph node metastases and the diagnosis of aggressive subtypes of PTCs.

In conclusion, in our experience 47.2% of lobectomies underwent completion surgery due to aggressive morphological parameters, which can be defined with the histological evaluation. The detection of enlarged lymph nodes may warrant an intraoperative examination to personalize surgical management. The detection of further malignant foci was not linked with differences in OS and/or DFS, mostly due to the indolent nature of the majrity of PTC and its subtypes. An accurate presurgical evaluation, performing US and FNAC, may help better tailor the surgical approach to the individual patient with thyroid cancer. Our initial evaluation with cytology offers the possibility to perform VE1-BRAF immunostaining on LBC stored material in order to recognize potentially more aggressive lesions in a pre-operative phase.

Funding

No competing financial interests exist for all the authors.

Conflict of interest statement

The authors have no conflict of interest. This work did not receive specific grant funding.

Ethical consideration

All patients consented to their procedure. We received institutional (Catholic University of the Sacred Heart) ethics approval for this study (n° 3382).

Authors contribution

EDR, LP, LML, planned concepted and designed the study, FP, PT, SC, LC, AC, FP, VF conducted the evaluation and acquisition of data, AP, GF, MR, CPL revised the draft and data

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