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Original Research

Partial thyroidectomy for papillary thyroid microcarcinoma: Is completion total thyroidectomy indicated?

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HIGHLIGHTS

- The best surgical approach for PTMC is still object of debate.
- Hemithyroidectomy may be adequate for low-risk patients, with no need for routine completion thyroidectomy.
- Total thyroidectomy or completion thyroidectomy is rather indicated in selected patients with risk factors for mortality and recurrence.
- Accurate patient selection is important to achieve the best results.

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ABSTRACT

Aim: Papillary thyroid microcarcinoma (PTMC) is increasing in incidence. Despite its excellent clinical outcomes, there is still debate regarding which surgical approach is more appropriate for PTMC, procedures including hemithyroidectomy (HT), total thyroidectomy (TT), and completion thyroidectomy (CT) after initial HT and histopathologic examination confirming a PTMC. Here we report our experience in the surgical management of PTMC.

Methods: We conducted a retrospective evaluation of all patients who received a postoperative diagnosis of PTMC between January 2001 and January 2016. Every patient was divided according to the type of surgery performed (TT or HT alone). Follow-up consisted of regular clinical and neck ultrasonographic examination. Clinical and histopathological parameters (e.g. age, sex, lesion size, histological features, multifocality, lymph node metastases, BRAF status when available) as well as clinical outcomes (e.g. complications rates, recurrence, overall survival) were analyzed.

Results: Group A consisted of 86 patients who underwent TT, whereas Group encompassed 19 patients who underwent HT. Mean follow-up period was 58.5 months. In Group A, one patient (1.2%) experienced recurrence in cervical lymph nodes with need for reoperation. In Group B, eight patients (42%) underwent completion thyroidectomy after histopathological examination confirming PTMC, while one patient (5.3%) developed PTMC in the contralateral lobe with need for reoperation at 2 years after initial surgery. Multifocality was found in 19 patients in Group A (22%). Of these, 14 presented bilobar involvement, whereas in 3 cases multifocality involved only one lobe. 1 patient in Group B (5.3%) presented with unilateral multifocal PTMC ($p = 0.11$).

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Conclusions: Low-risk patients with PTMC may benefit from a more conservative treatment, e.g. HT followed by close follow-up. However, appropriate selection of patients based on risk stratification is the key to differentiate therapy options and gain better results.

1. Introduction

Papillary thyroid carcinoma (PTC) accounts for about 80–90% of all thyroid cancers and its incidence has been increasing in the last three decades worldwide [1]. According to the American Cancer Society, about 64,300 new cases were estimated to be diagnosed in 2016 [2,3]. In Italy, PTC is the second most frequent cancer in women below 45 years of age and its incidence has almost doubled between 1991–1995 and 2001–2005 [3,4]. Despite this growth in incidence, mortality rate has remained the same (0.5 death per 100,000) and long-term prognosis is usually excellent, with 10-year survival rates up to 98% [3,5–7]. This upward trend in incidence can be easily explained by the wide availability and use of both neck ultrasonography and fine-needle aspiration cytology (FNAC), which allow an increased detection of papillary thyroid cancers measuring 1 cm or smaller, the so-called papillary thyroid microcarcinomas (PTMCs) [8–11]. Papillary carcinoma represents the most common type of thyroid carcinoma in patients >45 years old [2,8–11] and PTMC accounts for 49% of the overall increased incidence in thyroid cancer, as reported by the Surveillance Epidemiology and End Results (SEER) database [8,10]. PTMCs are also frequently identified incidentally upon histopathological examination of surgical specimens from presumed benign thyroid disease.

However, since PTMC generally exhibits an overall excellent prognosis, the most appropriate management of this disease remains a matter of debate and strategies range from observation alone [12] to surgical resection [13,14]. Still, there is no consensus yet about the extent of surgery ensuring oncologic completeness and low risk of complications and surgical approaches may consist of either simple lobectomy or total thyroidectomy, sometimes associated with neck dissection and/or postoperative radioactive iodine (RAI) therapy [6,9,15–21].

In order to better clarify whether the extent of surgery affects the outcomes of PTMC patients, we aimed to evaluate patients undergoing total thyroidectomy versus those undergoing simple hemithyroidectomy by comparing complications, reoperation rates, and overall survival.

2. Materials and methods

A retrospective analysis was carried out considering all papillary thyroid cancer operations performed at the General Surgery Department of the University Hospital of Treiste between January 2001 and January 2016. 105 consecutive patients with histological diagnosis of PTMC (major diameter $\leq$ 10 mm) were enrolled in the study and assigned to two independent groups according to whether they received total thyroidectomy (TT, Group A) or hemithyroidectomy (HT, Group B). Preoperative work-up consisted of full clinical examination, ultrasonography of the thyroid gland and regional lymph nodes, and FNAC. In most cases, PTMC was diagnosed preoperatively on FNAC analysis. In a minority of cases, diagnosis was incidental on pathological specimens after surgery for presumed benign thyroid disease. Patients with preoperative evidence of lymph node disease, those with extrathyroidal extension at clinical and/or ultrasound examination, and papillary tumors larger than 1 cm were not included in the analysis.

Total thyroidectomy (TT) was immediately performed in case of: malignant or suspicious lesions (TIR 5 or TIR 4 on FNAC) of $\leq$10 mm in diameter at preoperative ultrasound (US), multifocal PTC, bilateral goiters, prior neck irradiation, history of familial thyroid malignancies, age > 45 years, and/or presence of BRAF and/or nRAS mutation (when available) [22]. When nodal metastases were identified at the time of surgical procedure or during follow-up, the patients underwent either unilateral or bilateral central neck dissection (CND) or lateral neck dissection (LND) according to the American Thyroid Association (ATA) guidelines [23].

Patients were considered to be “low-risk” when presenting <2 cm papillary thyroid cancer without preoperatively apparent cervical lymph node metastases. Patients were classified as “high-risk” when unfavourable histological features (i.e. tall cells, oncogenic mutations as BRAF or nRAS, vascular invasion), extrathyroidal extension or spread of the cancer to the neck lymph node with potential risk factors (i.e. sex, age, and familiarity) were present [22–24].

HT was the treatment of choice for patients with preoperative TIR2 or TIR3 diagnosis [25], monolateral, unifocal, and intrathyroidal lesions, negative BRAF and/or nRAS status on FNAC, no history of previous head and neck irradiation, no clinical nor radiological evidence of nodal disease or distant metastases, no other specific risk factors. HT group included also 6 cases with BRAF negative, TIR 4 lesions (i.e. suspicious for malignancy), who underwent HT alone by choice of the single patients. Completion thyroidectomy (CT) was performed when definitive pathology found one or more of the following features associated with potentially aggressive PTMCs: multifocal disease with an overall sum of all lesions' diameters > 10 mm, actual size of papillary thyroid carcinoma >10 mm at definitive histology, microscopic extrathyroid extension, aggressive features (tall cell, columnar cell, or diffuse sclerosing variants).

Radioactive iodine (RAI) ablation therapy was administered on the basis of stage and prognostic risk factors [23–27]. In detail, patients received RAI therapy after total thyroidectomy or completion thyroidectomy in case of: aggressive histological subtypes (i.e. tall cells, columnar cells, or diffuse sclerosant variants), multifocality, extrathyroid invasion, and lymph node metastases, which potentially increase the risk for local recurrence and metastases. Successful thyroid ablation was defined by the disappearance of any visible area of uptake in the thyroid bed ($\leq$1%), and undetectable serum Tg levels of levothyroxine (TSH > 30μUI/mL).

All patients in Group An underwent long-term follow-up every 6 months for the first two years and on a yearly basis thereafter, whereas patients in Group B were followed every 6 months for the first three years and every year thereafter. Every follow-up visit consisted of clinical examination, cervical US, measurement of serum thyroglobulin (Tg) levels and anti-thyroglobulin antibodies (Ab-Tg).

Recurrence was defined by the presence of thyroid carcinoma within the thyroid bed, regional lymph nodes metastates, distant site metastases, or, in Group B patients, lesions to the contralateral lobe.

Histopathologic data (e.g. multifocality, aggressive features, extracapsular invasion, lymph node metastases) were recorded for

all patients and analyzed in order to determine whether completion thyroidectomy or total thyroidectomy were appropriate or should have been considered an overtreatment.

2.1. Statistical analysis

The statistical analysis was performed with GraphPad Software and by using Chi-squared test or Fisher's exact test, when appropriate. A *p*-value less than 0.05 was considered statistically significant.

3. Results

Analyzed data and results are summarized in Table 1. A total of 105 patients with PTMC underwent surgery over a 15-year period. Group A consisted of 86 patients (81.9%), 66 women and 20 men, mean age 54 years (range 12–77 years), who underwent TT. Group B consisted of 19 patients (18.1%), 14 women and 5 men, mean age 56 years (range 30–79 years), who underwent HT. 64 patients (61%) presented with TIR 4 or TIR 5 lesions, whereas 41 patients (39%) presented with TIR 2 or TIR 3 lesions on preoperative cytological diagnosis, respectively.

Multifocality was found in 19 patients in Group A (22%). Of these, 14 (16.3%) presented bilobar involvement, whereas 3 cases presented with unilateral multifocal PTMC. In Group B, 1 patient (5.3%) presented with multifocal unilobar PTMC ($p = 0.11$).

Mean tumor size was 6 mm (range 1–10 mm) in Group A and 5.3 mm in Group B (range 1–10 mm) (p = ns). BRAF mutation was tested preoperatively only in a minority of cases ($n = 16$ patients) and resulted positive in 9 patients with either TIR 3 or TIR 4 cytological diagnosis.

Either unilateral or bilateral central neck dissection (CND) was performed in 24 patients in Group A (27.9%) due to suspicious lymph nodes determined intraoperatively. Central nodal metastases were reported in 14 patients (58.3%).

8 patients out of 19 (42.1%) in group B underwent completion thyroidectomy at a mean time of 30 days after initial surgery on the basis of definitive histology. Reasons for completion thyroidectomy included: evidence of microscopic extrathyroid extension of tumor ($n = 2$ patients), multifocal unilateral disease ($n = 1$ patient), aggressive histopathologic variants ($n = 1$ patient with tall cells PTMC, $n = 1$ patient with diffuse sclerosing PTMC). Three patients required completion thyroidectomy after HT for personal preference on the basis of perceived risk of recurrence.

Mean follow-up period was 58.5 months (range 6–128 months) and consisted of regular physical examination and neck US imaging.

No significant difference was found between the two groups in terms of recurrence rates ($p = 0.33$). One patient in Group A (1.2%) developed regional lymph node recurrence 7 months after surgery and required a central and lateral neck dissection. To date, this patient is still alive and disease-free.

Morbidity rates were not significantly different between the two sets of patients, although incidence was slightly higher in the TT group (16.3% in group A vs. 10.5% in group B, respectively; ($p = 0.73$). Transient nerve palsy was reported in 4 cases (4.6%) in Group A and 1 case in Group B (5.3%), respectively ($p = 0.68$). Transient hypoparathyroidism, defined by serum Calcium levels <8.5 mg/dL), was recorded in 9 patients in Group A (10.4%) and in 1 patient in Group B (5.3%), respectively ($p = 0.18$). Permanent nerve damage was found only in 1 patient in Group A (1.2%, $p = 1.00$), whereas permanent hypoparathyroidism was not reported in any group.

The one patient in Group A who required further surgery for nodal recurrence suffered from transient hypoparathyroidism, whereas no complications occurred in Group B patients requiring completion thyroidectomy.

Postoperative RAI therapy was performed in 37 patients out of 86 in Group A (43%) and in 7 patients out of 10 in Group B after completion thyroidectomy (70%). The mean time-interval between thyroidectomy and ^{131}I administration for postsurgical remnant ablation was 3,5 months.

Mean disease-free survival was 72 months (range 6–192 months) in Group A and 78 months (range 8–137 months) in Group B, whereas the 5-year disease free survival was 98.8% and 93.7% respectively (p = 0.33). During the study period, 8 patients died for causes unrelated to thyroid cancer. In Group A, 3 patients died because of other cancers (lung cancer, gastric cancer, and cholangiocarcinoma, respectively) and 4 died for cardiovascular events, 96, 17, 83, 36, 58, 94 and 101 months after TT, respectively. In Group B, 1 patient died for a stroke at 137 months after HT. No PTMC-related death was recorded during the follow-up period.

Table 1
Age, sex, tumor features, pathologic findings and outcome in two groups of patients.

	Group A (TT)	Group B (HT)	*p value*
Number of patients (%)	86 (81.9%)	19 (18.1%)	<0.0001
Mean age (range)	54 (12–77)	56 (30–79)	-
Sex (M:F)	20:66	5:14	ns
Mean follow-up months (range)	57 (6–154)	64 (12–168)	ns
Mean tumor size in mm (range)	6 (1–10)	5.3 (1–10)	ns
Multifocal PTMC (%)	19 (22%)	1 (5.3%)	0.11
Bilateral PTMC (%)	14 (16.3%)	0	ns
Aggressive variants (%)	7 (8.1%)	2 (10.5%)	ns
Extrathyroid invasion (%)	11 (12.8%)	2 (10.5%)	ns
Lymph node metastases/lymph node dissection (%)	14/24 (58.3%)	0/0	–
Morbidity rates	16,3%	10.5%	0.73
Reoperation (%)	1 (1.2%)[a]	9 (47.3%)[b]	<0.0001
Transient nerve palsy (%)	4 (4.6%)	1 (5.3%)	0.68
Transient hypoparatiroidism (%)	9 (10.4%)	1 (5.3%)	0.18
Permanent nerve palsy (%)	1 (1.2%)	0	1.00
Permanent hypoparatiroidism (%)	0	0	/
Recurrence rate (%)	1 (1.2%)	1 (5.3%)	0.33
Disease free survival (range)	72 (6–192)	78 (8–137)	ns
5-year disease free survival	98.8% 93.7%	93.7%	0.33

Abbreviations: * TT = Total thyroidectomy; HT= Hemithyroidectomy.
[a] 1 lymph node metastases.
[b] 2 cases of PTMC in the controlateral lobe found at final pathology, no pathologic findings in the other specimens.

4. Discussion

Papillary thyroid microcarcinoma (PTMC) is increasing in incidence, partly due to increased detection determined by even more sensitive imaging techniques. However, both morbidity and mortality rates of thyroid cancer have not increased, suggesting that the upward trend in incidence more likely reflects an increased detection of subclinical disease which was previously discovered only casually on autopsy [8,26,27].

Prognosis is generally excellent, with 10-year survival rates of 90–95%. However, the best surgical management for PTMC is not established yet. ATA latest management guidelines [23] suggest that hemithyroidectomy in patients with PTMC may be appropriate treatment. Nonetheless, others Authors support only strict clinical observation [12]. Lin et al. [28], in a series of 7818 patients with PTMC, reported overall survival rates at 10 and 15 years of 96.6% and 96.3%, respectively, and a disease-specific survival of 99.9%. Yu et al. [29] achieved similar good results analyzing 18,445 patients with PTMC treated between 1988 and 2007, with 10 and 15-year overall survival of 94.6% and 90.7%, respectively, and disease-specific survival of 99.5%. These findings are supported by the meta-analysis of Roti et al. [30], who reviewed 17 series of PTMC reporting an overall distant recurrence rate of 0.37% and a cancer-related death of 0.34%.

The present study aimed to assess the most appropriate surgical management for PTMC patients, considering as primary goals the completeness of resection associated with acceptable morbidity risk, accurate tumor staging and adequate follow-up. In our study, we tried to determine whether immediate TT could be considered appropriate treatment compared to HT and whether CT was required after initial HT. In particular, we analyzed how many patients in the TT group presented on histopathologic examination multifocality lesions involving the contralateral lobe and/or aggressive features and/or extracapsular invasion and/or lymph node metastases. We further tried to determine in how many patients treated by means of a TT for a PTMC a simple HT could have been considered sufficient and adequate treatment. Last but not least, we evaluated the results of histopathological examination of the contralateral lobectomy in patients undergoing completion thyroidectomy, in order to determine whether the procedure represented an overtreatment.

The retrospective nature of the present study is a known potential bias. Obviously, it is important to differentiate patients diagnosed with PTMC preoperatively from those diagnosed after initial HT.

But, I underline, that the treatment option probably should be no different. In fact, until 2015 our local protocols, in accordance with our endocrinologists, (perhaps wrongly or maybe doing an overtreatment) suggested TT as a treatment of choice for all PTC (FNAC demonstrating malignancy) independently from size and localization (unilobar vs bilobar). The same local guidelines proposed HT for all patients with unilobar benign or indeterminate cytology (TIR 2 and 3). In case of thyroid cancer on definitive histology, CT was then proposed independently from the presence of extrathyroid extension or other acknowledged major risk factors. On the basis of ATA revised guidelines and availability of germline mutation assessment of BRAF and nRAS on FNAC, our local policy was updated after January 2015. To date, low-risk PTMC patients are proposed to undergo HT and, of course, to avoid a completion thyroidectomy in case of malignancy, discovered postoperatively, in absence of risk factors acknowledged risk factors.

Another limitation of the present study is the small sample size, hindering us to draw any definitive conclusion. Moreover, certain risk factors, as histological features, vascular invasion, extrathyroidal extension, and spread to regional lymph nodes, are difficult to estimate preoperatively. But, in all patients, other potential risk factors, i.e. sex, age, familiarity, BRAFV600E mutation status (when available), are evaluable preoperatively ant the extrathyroidal extension of tumor and/or the presence of suspicious lymph nodes are evident in most cases at the time of surgery.

According to the latest ATA Guidelines [23], HT should be considered the treatment of choice for PTMC patients. However, several Authors [12,31,32] now advocate clinical observation for these tumor considering the demonstrated indolent course of this tumor. Thus, the question of CT versus HT is possibly not worth asking and current guidelines suggest that CT for PTMC would not be indicated unless there is a history of head and neck irradiation and/or in presence of strong family history [23]. Nonetheless, the purpose of the study was to retrospectively evaluate our personal experience trying to determine whether immediate TT and CT after HT were to be considered appropriate surgical management of PTMC patients.

Another concern is represented by the fact that the study design is somewhat flawed since the two groups presenting different preoperative characteristics (i.e FNAC, and other specific risk factors) and different interventions were employed based on high or low risk characteristics. However, the analysis was retrospective in nature and data were collected on the basis of postoperative definitive histology (demonstrating PTMCs in both groups), thus enabling us to compare the two sets of patients.

The most interesting question that needs to be answered is what risk factors (molecular or demographic) are predictive of recurrence or multifocality in PTMCs, where a TT should be performed initially to avoid re-operation in a hostile surgical field. According to literature data, hereditary conditions, gender (Women are diagnosed with 3 of every 4 thyroid cancers), age (<45 years), and oncogenic mutation (BRAF/nRAS) on FNAC, can be predictive of recurrence or multifocality in PTMCs. Other factors that may be taken into account and be further analyzed could include low-iodine diet, radiation exposure, race (Caucasians and Asians are more likely to develop thyroid cancer), and association with breast cancer [22–24,33].

In literature, conflicting data have been reported with regard to the extent of surgery in order to ensure oncologic completeness. Hemithyroidectomy generally presents lower complication rates and determine a minimal impact on patient's life, allowing for the preservation of thyroid functions by avoiding the need for substitutive hormonal therapy in about 30–40% of cases [23,34,35]. However, HT present the risk for reoperation to the controlateral lobe after definitive histology and follow-up is usually limited because of the impossibility to perform radioiodine therapy and to check Tg levels.

Total thyroidectomy is a more radical surgical procedures which allows for: 1) a complete removal of the tumor, especially for multifocal/bilateral disease, with lower local recurrence, 2) an accurate staging of the disease, and 3) the possibility to both detect and treat any local or distant recurrence by means of RAI and serum Tg levels. This surgical approach has been corroborated by Baudin et al. and other more recent studies [36–39], which demonstrated that total thyroidectomy reduces the risk of recurrence and apparently improves survival rates. However, there is no definitive evidence in literature regarding the improvement in both recurrence and survival rates in low-risk patients treated with more aggressive approaches other than lobectomy [27,31,40–43]. Conversely, some authors believe these patients are being overtreated and exposed to higher risks of complications [44]. A recent large study analyzing data from the National Cancer Data Base between 1985 and 1998, for a total patients of 12,469 with PTMC, confirmed these remarks by demonstrating that the extent of surgery did not impact on recurrence nor on survival ($p = 0.24$ and

$p = 0.83$, respectively) [40]. Similar results have been reported by other studies, including Hay et al. (on 900 patients treated during a 60-year period) [31], Lee et al. (on 2014 patients treated for PTMC between 1986 and 2006) [41], Lin et al. (on 7818 patients) [28] and Ito et al. (on 2638 patients) [42]. Siassakos et al. [43] also reported no recurrences or deaths during a 6-year follow-up after HT for incidentally diagnosed PTMC patients.

Considering the indolent course of the disease, management of PTMC is still debated and recent proposals include close observation without surgical treatment [12,31,32]. Ito et al. [42] prospectively followed up a large group of PTMC patients who did not undergo any intervention and they concluded that these patients did not show a poorer prognosis when compared to those surgically treated. Additionally, a more recent observation trial by the same author showed that only 6.7% of low-risk PTMC ultimately become enlarged during a 5-year follow-up [45].

All these data substantiate the hypothesis that PTMC probably does not require an aggressive surgical management, which, on the contrary, may determine overtreatment and unnecessary morbidity. The present study is in accordance with these conclusion. We confirmed the benign course of PTMC after a mean follow-up period of 58.5 months, during which both groups presented excellent results in terms of disease-free and disease-specific survival, and no disease-specific death was observed. The study did not yield statistically significant differences in survival, recurrence and complication rates between the two groups, even if surgical complications occurred more frequently following total thyroidectomy than hemithyroidectomy. In our case series, one patient (5.3%) of Group B developed transitory hypoparathyroidism defined by calcium serum levels as low as 8.5 mg/dL at postoperative day one. The above mentioned patient was asymptomatic and required oral substitutive therapy for 48 h. No definitive hypocalcemia requiring long-life substitutive treatment was recorded.

The lack of differences in recurrence or survival between the two groups is in agreement with findings from other large series and recent guidelines suggest there is no need for completion thyroidectomy in low-risk patients, for whom close follow-up may be adequate. Nevertheless, for those high-risk PTMC cases which are more likely to recur and exhibit a worse prognosis compared with low-risk PTMCs, aggressive strategies should be indicated. Many studies have emphasized the need for a patient stratification based on the analysis of possible risk factors for mortality and recurrence (e.g. extrathyroidal invasion, aggressive histological subtypes, lymph node involvement, multifocality), in order to determine the most appropriate treatment by maximizing the benefits of surgery [29,42,46,47]. In fact, the vast majority of PTMC remain quiescent, causing no symptoms or threat to life. On the contrary, there are other situations where central lymph node metastases(CLNM) are described. Some tumor characteristics that are used to predict the CLNM and that justified a TT to PTMC patients. YI-Li Zhou et al. [48] reported in their series that CND needs to be considered in PTMC male patients, aged <50 years, or foci >7 mm based on preoperative US. Also in our series we founded a relatively high percentage of patients with preoperative diagnosis of simple PTMC who presented at the surgical exploration, central neck lymph nodes involvement (16.3%).

Another important aspect of PTCs is their multifocality. The multifocality is heterogeneous and it can involve either a single thyroid lobe or both. As reported by Anulekha Mary John et al. [49] in his retrospective study where a multifocal tumor was found in the 44,1% of the patients where 19,5% of multifocal disease was restrict to a single lobe. On the contrary, in other previous studies the incidence of bilateral PTMC reported is approximately 10–30% [9–11].

In our study, we found 16.3% of bilateral PTMC in group A whereas any patients of group B underwent completion thyroidectomy presented a contralateral papillary carcinoma on final histopathologic examination.

Based on our findings hemithyroidectomy would be maybe sufficient for low risks PTCs patients if followed by periodic follow up and ultrasound and after accurate selection.

5. Conclusions

In conclusion, the results of the present study do not support the routine TT in the treatment of PTMC patients while it is in accord with the latest ATA Guidelines suggesting to perform for “low-risk” PTMC the hemithyroidectomy. The risk for postoperative complication is significantly increased in TT patients, without clear evidence of reduction in recurrence or added benefit survival. Therefore, a less aggressive treatment may be adequate for most PTMCs, with no need for routine completion thyroidectomy. Although the best surgical approach for PTMC has to be adequately tailored, a careful patient selection is of paramount importance to determine the best treatment for each patient and achieve the better results. More prospective studies with longer follow-up periods are needed to further clarify the extent of surgery for PTMC and to recognize what risk factors (molecular or demographic) are predictive of recurrence or multifocality in PTMCs, where a total thyroidectomy should be performed initially to avoid re-operation in a hostile surgical field.

Ethical approval

Ethical approval was not requested.

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Author contribution

Chiara Dobrinja: Participated substantially in conception, design, and execution of the study and in the analysis and interpretation of data; also participated substantially in the drafting and editing of the manuscript.

Manuela Pastoricchio: Participated substantially in the execution of the study and in the analysis and interpretation of data; also participated substantially in the drafting and editing of the manuscript.

Marina Troian: Participated substantially in the analysis and interpretation of data; also participated substantially in the drafting and editing of the manuscript.

Francesca Da Canal: Participated substantially in conception, design, and execution of the study and in the analysis and interpretation of data.

Stella Bernardi: Participated substantially in conception, design, and execution of the study and in the analysis and interpretation of data.

Bruno Fabris: Participated substantially in conception, design, and execution of the study and in the analysis and interpretation of data.

Nicolò de Manzini: Participated substantially in conception, design, and execution of the study and in the analysis and interpretation of data; also participated substantially in the drafting and editing of the manuscript.

Conflicts of interest

All Authors have no conflict of interests.

Guarantor

Chiara Dobrinja.

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