HORMONES 2013, 12(4):529-536

Research paper

Bilateral versus unilateral papillary thyroid microcarcinoma: predictive factors and associated histopathological findings following total thyroidectomy

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ABSTRACT

OBJECTIVE: The extent of thyroidectomy for papillary thyroid microcarcinoma (PTMC) is debatable. This study investigated the rate and predictive factors of bilateral versus unilateral PTMC with the objective of identifying those patients who may benefit from total thyroidectomy. DESIGN: Between January 2001 and December 2008, 2019 patients who underwent total thyroidectomy were examined. A total of 319 patients diagnosed histopathologically as PTMC were included in the study. The predictive value of age at diagnosis, gender, tumor size, multifocality, lymph node metastasis, thyroid capsule invasion and nonincidental diagnosis using univariate and multivariate analyses were retrospectively analyzed. RESULTS: Of the 319 patients with PTMC, 77 (24.1%) presented bilateral disease. In univariate analysis, size of tumor ≥5mm ($p<0.001$), multifocality ($p<0.001$), lymph node metastases ($p<0.001$), thyroid capsule invasion ($p<0.001$) and nonincidental diagnosis ($p=0.002$) were significantly associated with bilaterality. In multivariate analysis, tumor size ($p<0.001$), multifocality of the primary tumor in the unilateral lobe ($p<0.001$) and lymph node metastasis ($p<0.001$) were independent predictive factors for bilateral PTMC. CONCLUSIONS: Tumor size ≥5mm and multifocality of the primary carcinoma in the unilateral lobe were independent risk factors for bilateral PTMC. Total thyroidectomy should be considered for these patients, which is of importance for the prediction of possible recurrence of disease.

Key words: Bilateral cancer, Papillary thyroid microcarcinoma, Predictive factors, Total thyroidectomy

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Received 17-01-2013, Accepted 24-03-2013

INTRODUCTION

Increased awareness of thyroid nodular disease, advances in diagnostic tools and refinements in histopathological criteria have resulted in a marked increase in the number of patients diagnosed with

thyroid cancer in developed countries. In 2011 there were 48,020 new cases of thyroid cancer and 2,620 deaths due to thyroid cancer in the United States, while American Cancer Society estimates for 2013 are 60,220 new cases and 1850 deaths.[1] Papillary thyroid carcinoma (PTC) is the most common thyroid follicular cell-derived malignancy and is considered to be a relatively indolent tumor from which death is rare. However, in the elderly and patients exposed to radiation PTC can behave aggressively.[2]

Papillary thyroid microcarcinoma (PTMC) is defined by the World Health Organization (WHO) as a PTC with a maximum diameter of ≤10 mm.[3] It is estimated that it accounts for up to 30% of all papillary thyroid cancers, although marked geographic differences in incidence rates have been noted.[4,5]

Most of PTMC are not detectable on clinical examination and they are only diagnosed incidentally during pathologic examination of the thyroid after surgery. The increased accuracy of pathologic examination, in particular thanks to the greater number and thinness of the anatomical slices, has led to more frequent pathologic diagnosis of incidental PTMC.[6]

Additionally, over the last few decades, the widespread use and the technical improvement of thyroid ultrasonography and fine-needle aspiration biopsy (FNAB) have resulted in a marked increase in the rate of preoperative diagnosis of PTMC.[7,8]

However, the management of PTMC, which are often undetectable by palpation, has become a controversial topic. The treatment may range from follow-up without surgery to total thyroidectomy with or without iodine treatment.[9-12]

Although total thyroidectomy is the treatment of choice followed by the majority of surgeons, unilateral lobectomy with radioactive remnant ablation (RRA) is favored for the treatment of PTMC, particularly by American authors.[13,14] In those patients with PTMC treated by lobectomy, most clinicians would argue for completion thyroidectomy if the risk of PTMC in the contralateral lobe was significant.

In this study, we retrospectively examined the incidence and related risk factors of PTMC with bilateral involvement in an endeavor to determine the independent predictors and to identify those PTMC patients who may benefit from total thyroidectomy.

PATIENTS AND METHODS

A total of 2019 patients underwent total thyroidectomy during the period between January 2001 and December 2008 in the Department of Otolaryngology in Venizeleio General Hospital of Heraklion, Greece. The medical records of all patients with a final pathologic report of PTMC were reviewed retrospectively.

All patients included in the study underwent standard total thyroidectomy. Surgical management of the patients was recommended upon referral to our hospital for heterogeneous reasons, such as suspicious thyroid malignancy, goiter, hyperthyroidism or compression of neighboring structures. Seventy-seven patients underwent total thyroidectomy for suspicious thyroid malignancy (clinically suspected PTMC), 218 for goiter, 16 for hyperthyroidism and 8 for compression of neighboring structures. All patients were operated on by four surgeons, and the pathological evaluation of thyroid specimens was performed by three pathologists at our institution. The entire gland and additional nodal tissue were evaluated from 1-mm-thick anatomical slices.

Of all total thyroidectomy patients, 588 (29.1%) presented with malignant neoplasms. Papillary carcinoma was diagnosed in 515 (25.5%) patients by histopathological examination, and 319 (15.8%) of these were microcarcinomas.

Inclusion criteria were adult age, standard total thyroidectomy and a histopathological diagnosis of papillary thyroid microcarcinoma according to the World Health Organization criteria.[3] Exclusion criteria were previous thyroid or parathyroid surgery, previous neck surgery, family history of cancer and history of neck radiation. The patients were divided into two groups: patients in Group 1 had tumor in both thyroid lobes (bilateral PTMC) and patients in Group 2 had tumor localized in only one thyroid lobe (unilateral PTMC).

Our database included age at the time of surgery, gender, surgical procedure, clinical characteristics and final pathological examination of the thyroid carcinoma, including multifocality, bilaterality, cervical lymph node involvement and thyroid capsule invasion.

The 7th edition of the American Joint Committee on cancer (AJCC) TNM classification of malignant tumors in 2010 was used to describe and categorize cancer stages and progression.

The clinical characteristics considered for statistical analysis were age (≤45 years versus ≥45 years), gender (male versus female) and clinically cervical lymph node metastases at the time of diagnosis (cN0 versus cN+).

The histopathological characteristics considered for statistical analysis were size of the tumor at its greatest diameter (≤5mm versus >5mm), histopathological evidence of autoimmune thyroid disease (Graves', Hashimoto disease, none), focality of tumor (right lobe versus left lobe, versus bilateral and unifocal versus multifocal).

Multifocal disease was defined as more than one tumor focus in the ipsilateral lobe of the primary tumor. Primary tumor was defined the tumor focus with the largest diameter.

Univariate analysis was performed with the Pearson Chi-square test and Fisher Exact test. The variables that were significantly associated with bilateral PTMC were included in a multivariate logistic regression analysis. Quantitative data are presented as mean±SD. A p value <0.05 was considered statistically significant. SPSS software (SPSS 17. Inc. Chicago, IL) was used for statistical analysis.

RESULTS

Of the 515 patients diagnosed with papillary thyroid carcinoma, 319 patients (62%) had tumor size measuring 10 mm or less at maximum diameter and met the inclusion criteria. Of the 319 patients with PTMC, 77 (24.1%) patients had bilateral disease, and 242 (75.9%) had unilateral. A total of 77 (22.7%) patients with PTMC were suspected preoperatively because of a positive FNAB, US findings, suspicious cervical lymph node and/or palpable nodule; these patients constituted the nonincidental group. Forty-three patients were diagnosed by a positive FNAB, 21 patients by US findings and 13 patients by a suspicious cervical lymph node and/or palpable nodule. On univariate analysis, bilaterality was significantly associated with tumor size ($p<0.001$), multifocality ($p<0.001$), lymph node metastasis ($p<0.001$), capsule invasion ($p<0.001$) and nonincidental diagnosis ($p=0.002$). There were no significant differences between the presence of contralateral carcinoma and gender, age and autoimmune thyroid disease ($p>0.05$) (Table 1).

We conducted multivariate logistic regression analysis of clinical and pathological factors. The results demonstrated that tumor size ($p<0.001$, OR = 3.18), multifocality ($p<0.001$, OR = 6.25) and lymph node metastases ($p<0.001$, OR = 3.37) showed a significant correlation with bilateral PTMC as independent risk factors (Table 2).

Of the 319 patients with PTMC, 261 (81.8%) were female and 58 (18.2%) were male and the male/female ratio was 1/4.1 (Table 1). The mean patient age at surgery was 50.31 ± 13.03 years (range from 18 to 88 years). There were 199 (62.4%) patients over 45 years of age and 120 (37.6%) patients under 45 years of age. The mean diameter of tumor was 4.02 ± 2.75 mm (range from 1 to 10 mm). The size of the thyroid cancer was 5 mm or less in 249 (78.1%) patients and larger than 5 mm in 70 (21.9%) patients. There was a significant difference in gender between tumor size groups ($p=0.010$). Of patients with tumors 5 mm or less, 209 (83.9%) were female and 40 (16.1%) were male. Among the patients with tumors greater than 5 mm, 49 (70%) were female and 21 (30%) were male, who demonstrated a statistically significant association of the size of tumor with male gender ($p<0.05$). In the group of patients with tumor size larger than 5 mm, we found that bilaterality was presented in 33 (42.9%) patients, multifocality in 44 (62.9%) patients, lymph node metastasis in 18 (25.7%) patients and capsule invasion in 16 (22.9%) patients. On univariate analysis, size of tumor was also strongly associated with bilaterality, multifocality, lymph node metastasis and capsule invasion ($p=0.001$).

In 123 (38.6%) patients the tumor was detected in the right lobe, in 119 (37.3%) patients in the left lobe and in 77 (24.1%) patients foci of tumor were detected in both lobes. The presence of multifocality was observed in 103 (32.3%) patients. Regarding the multifocality, a statistically significant difference was observed between bilateral and unilateral PTMC. Multifocality was found in 68 (88.3%) patients with bilateral PTMC and in 35 (14.5) patients with uni-

Table 1. Clinical and pathological characteristics of patients with bilateral versus unilateral PTMC (x^2 Pearson test was used – for normally distributed variables mean±SD is reported, for non-normally distributed variables median (range) is reported)

	Total patients (n=319)	Bilateral PTMC (n= 77)	Unilateral PTMC (n=242)	Percent (%) Total patients / Bilateral PTMC / Unilateral PTMC	P value
Gender					
Female	261	61	200	81.8 / 79.2 / 82.6 %	
Male	58	16	42	18.2 / 20.8 / 17.4 %	0.876
Age at diagnosis (years)					
Mean±SD	50.31± 13.03	50.10 ± 13.52	50.38 ± 12.90		
<45	120	31	89	37.6 / 40.3 / 36.8 %	
≥45	199	46	153	62.4 / 59.7 / 63.2 %	0.734
Tumor size (mm)					
Median (range)	3 (1-10)	6 (1-10)	3 (1-10)		
≤5mm	249	44	205	78.1 / 57.1 / 84.7 %	
>5mm	70	33	37	21.9 / 42.9 / 15.3 %	<0.001
Multifocality					
Yes	103	68	35	32.3 / 88.3 / 14.5 %	<0.001
No	216	9	207	67.7 / 11.7 / 85.5 %	
Autoimmunity					
Yes	201	54	147	67.0 / 70.1/ 60.7 %	0.175
No	118	23	95	33.0 / 29.9/ 39.3 %	
Lymph node metastasis					
Yes	34	21	13	10.7 / 27.3 / 5.4 %	<0.001
No	285	56	229	89.3 / 72.7 / 94.6 %	
Thyroid capsular invasion					
Yes	35	17	18	11 / 22.1 / 7.4 %	<0.001
No	284	60	224	89 / 77.9 / 92.6%	
Mode of diagnosis					
Nonincidental diagnosis (Clinically suspected)	77	31	46	24.1 / 40.3 / 19 %	0.002
Incidental diagnosis	242	46	196	75.9 / 59.7 / 81 %	

lateral PTMC. On univariate analysis, multifocality was significantly associated with autoimmune thyroid disease (p=0.005) and size of tumor (p<0.001), bilaterality (p<0.001), lymph node metastasis (p<0.001), capsule invasion (p=0.007). No association of multifocality with the age and gender of patients was observed (p>0.05).

Histopathological evidence of autoimmune thyroid disease was diagnosed in 201 (67%) of the patients. Bilaterality (p=0.014), multifocality (p=0.005), size of tumor >5 mm (p=0.007) and lymph node metastasis (p=0.002) were significantly related with the presence of autoimmune thyroid disease at univariate analysis. The presence of autoimmune thyroid disease did not correlate with gender and age (p>0.05).

Central neck compartment lymph node dissection was performed in 41 (12.9%) patients and in 34 (10.7%) of these patients histopathological nodal involvement was confirmed. At univariate analysis, risk factors for lymph node metastasis were clinically suspected PTMCs (p<0.001), the presence of bilaterality (p<0.001), tumor multifocality (p<0.001), autoimmune thyroid disease (p=0.001), capsule invasion (p<0.001) and size of tumor >5 mm (p<0.001). Age and gender were not associated with lymph node metastasis by univariate analysis (p>0.05). Multi-

Table 2. Independent risk factors for bilateral PTMC (multivariate analysis)

Variable	p value	Odds ratio – 95% confidence interval
Gender (male)	0.859	1.05 (0.48 – 2.28)
Age at diagnosis (years) ≥45 years	0.902	0.86 (0.46 – 1.62)
Tumor size (mm) >5 mm	<0.001	3.18 (1.64 – 6.17)
Multifocality	<0.001	6.25 (3.45 – 11.36)
Autoimmune thyroid disease	0.664	1.38 (0.74 – 2.60)
Lymph node metastases	<0.001	3.37 (1.43 – 7.96)
Thyroid capsular invasion	0.553	1.40 (0.55 – 3.57)
Nonincidental diagnosis	0.828	1.11 (0.50 – 2.42)

variate analysis showed that bilaterality (p=0.009), tumor multifocality (p=0.017), size of tumor >5mm (p=0.014), presence of capsule invasion (p=0.012) were independently predictive of lymph node metastasis.

Capsule invasion was detected in 35 (11%) patients. Statistically significant difference was found between the two age groups, where capsule invasion was present more frequently in patients under 45 years of age (p=0.022). Bilaterality (p<0.001), multifocality (p=0.002), tumor size (p<0.001) and lymph node metastasis (p<0.001) were also significantly associated with thyroid capsular invasion at univariate analysis. Gender and autoimmune thyroid disease were not associated with higher risk for capsule invasion (Table 1). Age of patient over 45 years (p=0.019) and both tumor size >5mm and lymph node metastasis (p<0.001) were found to be independent risk factors for capsule invasion by logistic regression analysis.

DISCUSSION

Recent advances in ultrasonography screening and US-guided FNAB have facilitated the detection and diagnosis of PTC and have resulted in a marked increase in the number of patients diagnosed with PTMC.[6,7] The rate of incidental PTMC that is undetected preoperatively ranges from 1.3% to 22% and varies widely, ranging in large series between 4.6 and 100%.[11,13] This range of incidental PTMC is likely due to the variation in the use of US and US-guided FNAB and to the experience with these techniques. It has been demonstrated that the biological behavior between incidentally diagnosed and clinically suspected PTMC tumors may vary significantly.[8,9]

While consensus guidelines recommend total thyroidectomy for PTC ≥1cm, the treatment of PTMC is still controversial. As recommended in the NCCN Clinical Practice Guidelines in Oncology: Thyroid carcinoma (v.2.2012): preoperatively detected bilateral PTMC are one of the indications for patients to be treated by total thyroidectomy. However, the optimal approach of surgical resection in cases with preoperatively undetected bilateral PTMC remains a topic of debate.

Studies had reported that the incidence of bilateral PTC ranged from 13% to 56%, that could be found in total thyroidectomy or completion thyroidectomy, and incidence of bilateral PTMC was approximately 10-30%.[14-17] In our study, 24.1% of PTMC patients who underwent total thyroidectomy had contralateral PTMC. This rate was consistent with other reports.[11,14-16]

In our study, on univariate analysis, bilaterality was significantly associated with the size of tumor (p<0.001), multifocality (p<0.001), lymph node metastasis (p<0.001), capsule invasion (p<0.001) and nonincidental diagnosis (p=0.002) (Table 1). We also demonstrated that multifocality of the primary tumor in the ipsilateral lobe, the size of primary tumor >5mm and the lymph node metastasis at diagnosis were independent predictors for the presence of an incidental contralateral papillary carcinoma and for higher frequency rates of bilaterality (Table 2).

Size of tumor

Several authors have reported that the presence of contalateral papillary thyroid carcinoma appeared to be unrelated to the size of the primary tumor.[16,18,19] By contrast, our study found that primary tumor ≥5mm was an independent predictive factor for contralateral PTMC. This finding could be explained by the fact that our study included an large number of PTMC patients who all underwent total thyroidectomy compared with other studies that had a relatively smaller sample of patients and only a fraction of the cases underwent total thyroidectomy.[18,20] Additionally, Zhou et al.

reported that tumor size ≥7 mm based on US was an independent predictive factor for bilateral PTMC.[21]

Multifocality

Previous studies have reported comparable findings to our study, suggesting that ipsilateral multifocal disease was predictive of papillary thyroid carcinoma in the contralateral lobe.[18-22] The multifocal location of the tumor in PTMC is reported to be a risk factor for lymph node metastasis, distant metastases and local recurrence.[9,13,15] Multifocality is usually found in approximately 30-40% of PTMC cases.[14,15,23] Both multifocality and lymph node metastasis at diagnosis increased the risk of lateral nodal recurrence, with 11% of multifocal tumors exhibiting recurrence, compared to 4% of unifocal tumors.[14] Additionally, the presence of PTMC foci in both thyroid lobes constituted a risk factor that increased the rate of locoregional recurrence.[14,19,24]

Lymph node metastasis

The presence of lymph node metastasis in patients with PTMC is frequent. It ranges from 5.2% to 44.2% in those patients subjected to therapeutic or necessary dissection, and as high as 29% to 64% in patients subjected to prophylactic or elective dissection.[25] Our study demonstrated that lymph node metastasis at diagnosis was an independent predictor of papillary thyroid carcinoma in the contralateral lobe. Our results confirmed the finding from other studies indicating that multifocality and bilaterality are predictive factors affecting lymph node metastasis.[9,15,25]

In our study, the incidence of lymph node metastasis was 10.7% overall and decreased to 5.4% in patients with unilateral PTMC. In contrast, in patients who presented foci in both thyroid lobes, the incidence of lymph node metastasis was elevated to 27.3%. A possible explanation for this result is that bilateral PTMCs were more frequently diagnosed preoperatively after a positive cytology with US-FNAB, or following diagnosis of a cervical nodal metastasis in clinically suspected PTMC (Table 2). In addition, the size of tumor in bilateral PTMC was statistically significantly larger than the size in unilateral PTMC (Table 1). Several authors have reported that PTMCs >5mm had more frequently lymph node metastasis compared with PTMCs ≤5mm.[23,26-28] Others stated that there was no difference in aggressiveness between the patients with PTMCs ≤5mm and those with PTMCs >5mm.[15,29]

Therapy

Considerable debate has centered on the clinical significance of PTMC and if these tumors should be managed as aggressively as other PTC. It is well known that PTMC have an excellent prognosis with mortality rates of 0-1%. Therefore, unilateral lobectomy for PTMC patients has been advocated by some authors to avoid increased risk of permanent recurrent laryngeal nerve injury and permanent hypocalcemia.[14] Patients undergoing lobectomy are often subjected to a potential second surgery with a higher rate of complications and nearly 50% of these may require hormone replacement therapy anyway.[30,31]

Previous studies have maintained that some PTMCs may have an aggressive behavior and can cause local and regional recurrences, as well as cervical lymph node metastases.[14] Hay et al reported that 80% of recurrences were within cervical lymph nodes, with most of the remainder representing recurrence in the contralateral nonresected lobe or in the soft tissues of the thyroid bed.[14] Higher recurrence rates were seen in patients with multifocal tumors and in node-positive patients. Another risk factor for locoregional recurrence in PTMC patients was the extent of initial surgery.[14] The recommended strategy of Mayo Clinic suggested that surgery should ensure that all primary tumors are resected and that potential tumor-foci in the contralateral lobe and lymph node of the central neck compartment are resected at the same operation if this can achieved without unjustified risk.

The same surgical strategy is adopted by our department. We prefer total thyroidectomy to lobectomy because of the likelihood of bilaterality and also because in the cases where a completion thyroidectomy was required, the risk of complications was much higher. Moreover, the advantages of total thyroidectomy are the improved ablation of the tumor, greater sensitivity of thyroglobulin, allowance for use of I-131 in the detection of metastasis and recurrence and also lower local recurrence rate because all potential foci in both lobes are removed.[4,28] Of note, total thyroidectomy allows the pathologist to assess the entire thyroid gland and to diagnose bilaterality,

multifocality and histological variants of tumor and extrathyroidal extension.

Finally, an important reason for considering total thyroidectomy over lobectomy is the reported low frequency of permanent recurrent laryngeal nerve damage or permanent hypocalcemia when performed by experienced surgeons.[14,32] The complications rate in this series was relatively low, with 11 patients (3.4%) experiencing transient hypocalcemia, 3 patients (0.9%) experiencing permanent hypocalcemia and 4 patients (1.2%) presenting transient unilateral recurrent laryngeal nerve palsy. The low rate of complications associated with the complete surgery of bilateral resection, which eliminates the risk of cancer recurrence observed with unilateral lobectomy when tumor bilaterality exists, are the main rationale for our center adopting total thyroidectomy as the treatment of choice for PTMC patients.

The limitations of our study include the retrospective nature of analysis with patients from a single institution, the fact that histology was interpreted by three pathologists, the absence of post-operative scan to assess the completeness of total thyroidectomy, the exclusion of patients with a family history of cancer and previous neck radiation and the lack of patients' follow-up.

CONCLUSION

The high rate (24.1%) of bilateral involvement of PTMC patients in this study determined our strategy to carry out surgical resection. Tumor size ≥5mm and multifocality of the primary carcinoma in the unilateral lobe were independent risk factors for bilateral PTMC. We suggest that total thyroidectomy should be considered in PTMC patients in whom tumor size ≥5mm and multifocality are detected preoperatively, since this approach is important for the prediction of possible recurrence of disease.

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