TÜBİTAK

Turkish Journal of Medical Sciences

http://journals.tubitak.gov.tr/medical/

Research Article

Turk J Med Sci
(2017) 47: 1723-1727
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doi:10.3906/sag-1702-99

Prediction of central lymph node metastasis in patients with thyroid papillary microcarcinoma

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Received: 16.02.2017 • **Accepted/Published Online:** 02.07.2017 • **Final Version:** 19.12.2017

Background/aim: The purpose of this study was to analyze the clinicopathological characteristics of patients with papillary thyroid carcinoma (PTC) and papillary thyroid microcarcinoma (PTMC) and predictive factors for central lymph node metastasis (CLNM).

Materials and methods: Patients diagnosed as having PTC and PTMC were evaluated. Clinical and laboratory parameters were recorded.

Results: The mean age at diagnosis was 47.3 ± 11.9 years. Of all 223 patients, 91 (40.8%) had lymph nodes removed, 29 of whom had lymph node metastasis and 24 of whom had only CLNM. Univariate analysis revealed that central lymph node metastasis was associated with male sex, presence of bilaterality, presence of extrathyroidal extension, and tumor size ($P = 0.033$, $P = 0.027$, $P < 0.001$, $P < 0.001$, respectively). However, multivariate logistic regression analysis showed that sex, age, tumor size, multifocality, bilaterality, extrathyroidal extension, clinical suspicion, and chronic lymphocytic thyroiditis were not significantly correlated with an increased risk for CLNM.

Conclusion: Lymph node metastasis is known to be a significant predictor of locoregional recurrence in patients with PTC and PTMC. Further prospective studies are needed to identify the extent of surgery such as central lymph node dissection in patients with PTC or PTMC.

Key words: Papillary thyroid microcarcinoma, central lymph node metastasis

1. Introduction

Papillary thyroid carcinoma (PTC) is the most common malignancy of the thyroid gland. Papillary thyroid microcarcinoma (PTMC) is a subtype of PTC defined as PTC with a maximum tumor diameter of 10 mm or less (1). Several studies have reported that PTMC is determined in up to 35.6% of autopsy materials, and up to 37.3% of PTMCs are associated with cervical lymph node metastasis (1–3). In recent years, the number of patients with PTMC has been increasing because of the use of high-resolution ultrasonography (USG) and fine-needle aspiration biopsy. Despite the fact that PTMC is usually associated with good prognosis, regional lymph node metastasis is not uncommon (4). Moreover, several studies have demonstrated lymph node metastases at presentation, locoregional recurrence during follow-up, and rarely distant metastases and even cancer-related deaths (5–8). Central lymph node metastasis (CLNM) is frequently diagnosed with microscopic lymph node metastasis in surgical specimens. In PTMC, the prevalence of subclinical CLNM has been detected as 30%–65% (4,9,10). Previous studies suggested the use of prophylactic central lymph node dissection (CLND) in patients with PTMC (11,12); however, this approach remains a controversial matter. Therefore, determination of predictive factors for CLNM is important to avoid unnecessary CLND in patients with PTMC. To improve the diagnostic accuracy in PTMC, many authors used a combination of clinicopathologic and USG characteristics. Therefore, the purpose of this study was to investigate the predictive factors for CLNM among a group of patients with surgically proven PTMC or PTC.

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2. Materials and methods

2.1. Study population

We conducted a retrospective study involving 223 patients with PTC who underwent definitive primary surgical therapy between January 2010 and December 2014. All patients had no history of thyroid or neck surgery for nonthyroidal cancer, as well as no neck irradiation. Medical records and radiologic and pathologic reports were analyzed. Papillary thyroid carcinoma measuring 10 mm or less in diameter was classified as PTMC. Data collected included age, sex, preoperative clinical suspicion of cancer based on USG findings, tumor size, multifocality, bilateral disease, chronic lymphocytic thyroiditis, extrathyroidal extension, central or lateral lymph nodes with metastatic carcinoma, and type of surgery (thyroidectomy with or without central lymph node dissection). Tumor size was defined as the largest dimension. Multifocality was defined as more than 1 focus of tumor within the thyroid. Bilateral tumors were defined as tumors existing in both thyroid lobes.

2.2. Statistical analysis

The statistical analyses were performed using SPSS 18.0 (SPSS Inc., Chicago, IL, USA). Normally distributed data are expressed as mean ± SD and were compared using the t-test. Categorical variables are expressed as percentage and were compared using the chi-square test or Fisher's exact test as appropriate. Nonparametric variables were analyzed using the Mann-Whitney U test. In the statistical analyses, $P < 0.05$ was considered significant.

3. Results

The study population included 223 patients, the majority whom were female (173, 77.6%). The mean age at diagnosis was 47.3 ± 11.9 years (range: 17–77 years) and 124 (55.6%) patients were aged more than 45 years. Table 1 lists the clinical and pathologic characteristics between the PTC and PTMC groups.

A total of 208 (93.3%) patients underwent total or near total thyroidectomy, and 15 (6.7%) had a lobectomy followed by a complete thyroidectomy at a later date.

Ninety-one (40.8%) of the 223 patients had lymph nodes removed, 86 had central lymph nodes only removed, 3 had lateral lymph nodes only removed, and 2 had both central and lateral lymph nodes removed. Of these 91 patients, 29 had lymph node metastasis and 24 had only central lymph node metastasis (CLNM).

Of the 88 patients who had central lymph nodes removed, 26 (29.5%) had CLNM. Univariate analysis revealed that central lymph node metastasis was associated with male sex, presence of bilaterality, presence of extrathyroidal extension, and tumor size ($P = 0.033$, $P = 0.027$, $P < 0.001$, $P < 0.001$, respectively). However, the multivariate logistic regression analysis showed that sex, age, tumor size, multifocality, bilaterality, extrathyroidal extension, clinical suspicion, and chronic lymphocytic thyroiditis were not significantly correlated with an increased risk for CLNM (Table 2).

Among the 141 patients with PTMC, 47 had only CLND, 7 (14.9%) of whom had CLNM. Twenty-six patients had CLNM, 19 had PTC, and 7 had PTMC. There was a significant difference in CLNM between patients with PTC and PTMC ($P < 0.001$).

4. Discussion

Differentiated thyroid carcinoma is the most common endocrine malignancy. We investigated clinical and pathologic features in patients with PTC and PTMC. PTMC is considered an indolent disease that has excellent prognosis with a mortality of about 1% and recurrence or persistence of only 1.4%–10.5% (4,5,13–15). On the other hand, the potential aggressiveness of PTMC has been reported in some studies (5–7,16).

The treatment for PTMC continues to be a topic of debate in the literature. Some authors choose complete thyroidectomy plus lymph node dissection, whereas others choose observation in the event of a solitary PTMC found incidentally on lobectomy/thyroidectomy (17). Central lymph node metastasis is still a risk in patients with PTC or PTMC; we found that 29.5% of all patients had CLND. Despite the fact that many studies have shown that lymph node metastasis in PTMC is one of the main predictors of recurrence (18–20), there is no consensus as to whether prophylactic neck dissection should be routinely included in the surgical treatment. The American Thyroid Association guidelines recommend inclusion of neck dissection for PTC only in the setting of clinically evident lymph node metastasis (21). However, the reported incidence of lymph node metastasis in PTC has ranged widely from 20% to 90% (22). Routine prophylactic CLND might be associated with significantly higher morbidities, such as recurrent laryngeal nerve injury and hypoparathyroidism (23,24). CLND can be achieved with low morbidity by experienced thyroid surgeons (25,26).

In our study, male sex, tumor size, age, multifocality, extrathyroidal extension, clinical suspicion, and chronic lymphocytic thyroiditis were not predictive of CLNM. Vorasubin et al. (27) recently demonstrated that large, multifocal, and capsularly or lymphovascularly invasive PTMC was significantly associated with at least a 1.93 times greater risk of metastasizing than were smaller, solitary, and noninvasive tumors. Another study by Siddiqui et al. (28) showed that younger age (age < 45 years), multifocality,

Table 1. Patient characteristics.

Variable	PTMC (n = 141)	PTC (n = 82)	P
Sex, n (%)			
Female	116 (67.1)	57 (32.9)	0.028
Male	25 (50.0)	25 (50.0)	
Age at diagnosis, years, mean ± SD	48.2 ± 10.9	45.8 ± 13.4	0.148
Age, n (%)			
≤45 years	56 (56.6)	43 (43.4)	0.065
>45 years	85 (68.5)	39 (31.5)	
Tumor size, mm (range)	0.5 (0.1–1.0)	2.0 (1.1–8.5)	
Multifocality, n (%)			
Absent	100 (70.9)	51 (62.2)	0.179
Present	41 (29.1)	31 (37.8)	
Bilaterality, n (%)			
Absent	116 (82.3)	56 (68.3)	0.017
Present	25 (17.7)	26 (31.7)	
Chronic lymphocytic thyroiditis, n (%)			
Absent	104 (73.8)	65 (79.3)	0.354
Present	37 (26.2)	17 (20.7)	
Extrathyroidal extension, n (%)			
Absent	130 (92.2)	64 (78.0)	0.002
Present	11 (7.8)	18 (22.0)	
Clinical suspicion on preoperative USG, %			
Unsuspected	61.0	64.4	0.708
Suspected	39.0	35.6	
Central lymph node dissection, n (%)			
Absent	94 (66.7)	41 (50.0)	0.014
Present	47 (33.3)	41 (50.0)	
Central lymph node metastasis, n (%)			
Absent	134 (95.0)	63 (76.8)	<0.001
Present	7 (5.0)	19 (23.2)	

and extrathyroidal extension were predictors of CLNM. Our data showed that male sex and tumor size were not predictive for CLNM, in contrast to findings by others (18,29,30). In addition, Siddiqui et al. reported that the risk of lymph node metastasis in incidental PTMC was not significantly different compared with known/suspected PTC (28). Therefore, physicians must be aware of central or lateral lymph node metastasis when planning treatment for PTMC.

The limitation to our study is the small number of overall patients and the small number of patients with resected lymph nodes. In addition, we did not analyze data from the long-term follow-up period such as disease recurrence and disease-free survival.

Table 2. Multivariate logistic regression analysis for clinical and pathologic features predictive of CLNM.

	CLNM		
Risk predictor	OR	95% CI	P-value
Age	0.912	0.772–1.078	0.280
Sex	0.949	0.093–9.703	0.964
Tumor size	1.841	0.673–5.039	0.235
Multifocality	0.581	0.046–7.404	0.676
Bilaterality	0.220	0.014–3.538	0.286
Chronic lymphocytic thyroiditis	3.233	0.338–30.92	0.308
Extrathyroidal extension	0.331	0.017–6.372	0.464
Clinical suspicion	0.194	0.016–2.390	0.201

In conclusion, PTMC can metastasize to central or lateral lymph nodes. Lymph node metastasis is known as a significant predictor of locoregional recurrence. Further prospective studies are needed to identify the extent of surgery such as CLND in patients with PTC or PTMC.

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