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Factors Influencing Central Neck Lymph Node Metastasis in Patients with Papillary Thyroid Microcarcinoma

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Purpose: A papillary thyroid microcarcinoma (PTMC) measures 1 cm or less in diameter. The diagnosis, and thus the apparent incidence, of PTMC has recently increased owing to an increase in the detection of subclinical small and low-risk carcinomas with ultrasonography and fine needle aspiration cytology. However, central neck lymph node metastasis (CLNM) can occur in patients with PTMC. We evaluated the factors influencing CLNM in patients with PTMC.

Methods: We reviewed medical records including clinical information and pathologic reports, and analyzed 622 patients with PTMC who underwent thyroid surgery from January 2002 to December 2012.

Results: CLNM was detected in 119 patients (19.1%) of the 622 with PTMC. Lymph node metastasis occurred more frequently in males (P=0.025), and those with bilateral tumors (P=0.016), more than two tumors (P=0.035), tumor size greater than 5 mm (P＜0.001), and lymphovascular invasion (P=0.024). There were no statistically significant differences in age and capsular invasion. Multivariate analysis showed that significant factors affecting lymph node metastasis included age at operation (odds ratio [OR]=0.647, 95% confidence interval [CI]=0.422～0.990, P=0.045), sex (OR=0.489, 95% CI=0.268～0.891, P=0.020), tumor size (OR=3.034, 95% CI=1.761～5.224, P＜0.001), and lymphovascular invasion (OR=15.036, 95% CI=1.450～155.911, P=0.023).

Conclusion: Age less than 45 years, male sex, tumor size greater than 5 mm, and lymphovascular invasion were risk factors associated with CLNM.

Key Words: Thyroid, Papillary carcinoma, Microcarcinoma, Lymph node metastasis

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INTRODUCTION

Papillary thyroid microcarcinoma (PTMC) is defined as a papillary thyroid carcinoma (PTC) measuring 10 mm or less in its greatest diameter according to the World Health Organization classification system for thyroid tumors.(*1*) The increasing use of thyroid ultrasound (US) and US-guided fine needle aspiration (FNA) have led to an increased detection rate of PTMC.(*2,3*) Although PTMC has an excellent prognosis, these tumors are associated with a 1% disease-related mortality rate, 5% lymph node recurrence rate, and 2.5% distant metastasis rate.(*4*) Most recurrences are diagnosed in the thyroid bed or neck lymph nodes, and central neck lymph node metastasis (CLNM) is an important risk factor for recurrence.(*5*)

American Thyroid Association (ATA) guidelines indicate that differentiated thyroid cancer (DTC) should be considered for central neck dissection when metastatic lymph nodes are evident (cN1) in a preoperative US or are palpable on physical examination.(*6,7*) However, prophylactic central lymph node dissection (CLND) in patients with PTMC without evident lymph node metastasis (LNM)

remains controversial. Prophylactic CLND has little prognostic value and efficacy.(8) Moreover, the accuracy of preoperative US for the identification of CLNM is limited owing to the overlying thyroid gland, and CLNM does not appear abnormal on preoperative imaging or by inspection at the time of surgery. Therefore, determination of the clinicopathologic factors associated with CLNM is significant in the decision to perform prophylactic CLND.

The aim of this study was to identify the factors that predict subclinical CLNM in patients with PTMC and to assist in decision-making for CLND.

METHODS

We conducted a retrospective review of data from a single center, in which a single surgeon operated on a total 1,573 patients with PTC at single institution from January 2002 to December 2012. We included PTMC patients according to pathologic reports regardless of the type of surgery (lobectomy, near-total thyroidectomy, or total thyroidectomy), and identified 622 patients who underwent therapeutic or prophylactic CLND with PTMC. All patients were diagnosed with PTMC preoperatively by ultrasonography and fine-needle aspiration biopsy. Patients with bilateral PTMC underwent total thyroidectomy or near-total thyroidectomy and bilateral prophylactic CLND, while patients with unilateral PTMC underwent near-total thyroidectomy or unilateral lobectomy plus ipsilateral CLND. All patients underwent therapeutic or prophylactic CLND. We reviewed clinical and pathologic information of the 622 enrolled patients. Patients were divided into two groups according to central compartment lymph node status. We investigated the relationship between CLNM and clinical and pathological factors such as age at diagnosis, sex, bilaterality, multiplicity, type of operation, tumor size, node metastasis, capsular invasion, and lymphovascular invasion.

Statistical analysis was performed using SPSS ver. 21.0 (SPSS Inc., Chicago, IL, USA). Univariate analysis was performed using Pearson's chi-square test or Fisher's exact test. Multivariate analysis was performed using logistic regression analysis. A P value of less than 0.05 was considered statistically significant.

RESULTS

Of 622 patients included in this study, 557 were female and 65 were male, with a mean age of 52 years. The clinicopathologic features are presented in Table 1. The numbers of cases confined to one lobe were 350 (56.3%). Multifocal PTMC was present in 322 cases (51.8%). A total of 239 (38.4%) underwent lobectomy, 250 (40.2%) had near-total thyroidectomy, and 133 (21.4%) had total thyroidectomy. The tumor diameter measured less than 5 mm in 198 cases (31.8%) and more than 5 mm in 424 cases (68.2%), in pathology reports. Capsular and lymphovascular invasion were found in 20 cases (3.2%) and 4 cases (0.6%), respectively. Among the 622 patients, 119 (19.1%) were found to have CLNM on final pathological exami-

Table 1. Clinicopathologic features in patients with papillary thyroid microcarcinoma (N=622)

Factors	Number of patients	Percent (%)
Age at operation		
<45 years old	289	46.5
≥45 years old	333	53.5
Sex		
Male	65	10.5
Female	557	89.5
Tumor location		
Unilateral	350	56.3
Bilateral	272	43.7
Multiplicity		
1	300	48.2
≥2	322	51.8
Type of operation		
Lobectomy	239	38.4
Near-total thyroidectomy	250	40.2
Total thyroidectomy	133	21.4
Tumor size (largest)		
<0.5 cm	198	31.8
0.5~1 cm	424	68.2
Node metastasis		
No	503	80.9
Yes	119	19.1
Capsular invasion		
No	602	96.8
Yes	20	3.2
Lymphovascular invasion		
No	618	99.4
Yes	4	0.6

Table 2. Comparison of risk factors according to lymph node metastasis in patients with papillary thyroid microcarcinoma (N=622)

Factors	No central neck lymph node metastasis (N=503)	Central neck lymph node metastasis (N=119)	P value*
	Number of patients (%)	Number of patients (%)	
Age at operation			0.102
<45 years old	227 (45.1)	62 (52.1)	
≥45 years old	276 (54.9)	57 (47.9)	
Sex			0.025
Male	46 (9.1)	19 (16.0)	
Female	457 (90.9)	100 (84.0)	
Tumor location			0.016
Unilateral	294 (58.4)	56 (47.1)	
Bilateral	209 (41.6)	63 (52.9)	
Number of tumors			0.035
1	252 (50.1)	48 (40.3)	
≥2	251 (49.9)	71 (59.7)	
Type of operation			0.002
Lobectomy	210 (41.7)	29 (24.4)	
Near-total thyroidectomy	192 (38.2)	58 (48.7)	
Total thyroidectomy	101 (20.1)	32 (26.9)	
Tumor size (largest)			<0.001
<0.5 cm	180 (35.8)	18 (15.1)	
0.5~1 cm	323 (64.2)	101 (84.9)	
Capsular invasion			0.068
No	490 (97.4)	112 (94.1)	
Yes	13 (2.6)	7 (5.9)	
Lymphovascular invasion			0.024
No	502 (99.8)	116 (97.5)	
Yes	1 (0.2)	3 (2.5)	

*<0.005, statistically significant.

nation, while 503 (80.9%) did not have CLNM.

The clinicopathological characteristics of patients are summarized for the CLNM-positive and CLNM-negative groups in Table 2. The factors associated with CLNM were male sex (P=0.025), bilateral tumor location (P=0.016), presence of more than two tumors (P=0.035), type of operation (P=0.002), tumor size greater than 5 mm (P<0.001), and lymphovascular invasion (P=0.024). There were no statistically significant differences in age and lymphovascular invasion.

Multivariate analysis was performed to determine whether these parameters were independently correlated with CLNM. In logistic regression analysis, the factors associated with CLNM were age greater than 45 years (odds ratio [OR]=0.647, 95% confidence interval [CI]=0.422~0.990, P=0.045), female sex (OR=0.489, 95% CI=0.268~0.891, P=0.020), tumor size greater than 5 mm (OR=3.034, 95% CI=1.761~5.224, P<0.001) and lymphovascular invasion (OR=15.036, 95% CI=1.450~155.911, P=0.023) (Table 3).

Table 3. Logistic regression analysis for lymph node metastasis in patients with papillary thyroid microcarcinoma (N=622)

Factors	OR	95% CI
Age over 45 years old	0.647	0.422~0.990
Female gender	0.489	0.268~0.891
Bilateral tumor location	1.530	0.663~3.529
Number of tumors (≥2)	1.105	0.474~2.575
Tumor size (0.5~1 cm)	3.034	1.761~5.224
Capsular invasion (present)	2.312	0.876~6.097
Lymphovascular invasion (present)	15.036	1.450~155.911

OR = Odds ratio; CI = confidence interval.

DISCUSSION

The incidence of thyroid cancer has increased mainly because of the increased incidence of PTMC, as a result of

imaging procedures such as US of the neck and FNA, but routine CLND in the treatment of PTMC remains controversial.(*9*) Therapeutic CLND to reduce persistence and recurrence is always necessary in PTMC patients, whereas prophylactic CLND remains a subject of considerable debate,(*10*) because there are no randomized controlled trials indicating that routine prophylactic CLND affects recurrence or survival rates of PTMC. In addition, whether prophylactic CLND increases the risk of complications such as hypocalcemia and recurrent laryngeal nerve palsy remains controversial.

Because of stepwise progression of lymph node metastasis from the central to the lateral compartment, it is important to determine whether CLNM is present. One study reported that 64% of PTMC patients develop CLNM.(*8*) However, 19.1% of all patients in this study had CLNM.

The usefulness of preoperative US in the evaluation of CLNM is often limited due to surrounding structures. Thus, it is important to identify preoperative factors predictive of CLNM when developing an individualized treatment plan. Moreover, the identification of such predictive factors is important to avoid unnecessary neck dissection in PTMC patients, particularly those with an indication for prophylactic CLND.

The factors predictive of CLNM in patients with PTMC are not well defined. However, it is generally accepted that prognosis depends on sex, tumor multifocality, capsular invasion, and tumor size.

The cut-off age of 45 years is widely used as a clinical marker for prognosis.(*11*) However, its predictive value in PTMC has been uncertain. Previous studies reported that age was not associated with LNM in patients with PTMC.(*12,13*) On the other hand, some authors recommend prophylactic CLND for patients aged more than 45 years, because these patients have a decreased capacity for radioactive iodine (RAI) uptake, and adjuvant RAI treatment may not be effective.(*14*) The present study showed that age less than 45 was predictive of CLNM.

Male sex has previously been suggested as an important indication for prophylactic LND.(*14,15*) In this study, male sex was independently predictive of CLNM, in agreement with previous reports. Although the incidence of PTMC was higher among females in an epidemiological survey, males require specialized neck examinations to enable the early detection of thyroid tumors. Despite the small tumor size, once a malignant diagnosis is confirmed in a male patient, our results indicate that CLND might be necessary.

PTMC is often multifocal, and some studies showed that multifocality was associated with tumor recurrence.(*16,17*) Tumor bilaterality in PTC is traditionally considered an indication for total or near-total thyroidectomy, but few data specifically examining the prognostic implications of bilateral disease have been reported. Wang et al.(*18*) found that patients with bilateral PTC were more likely to have larger tumor size, extrathyroidal invasion, LNM, and a more advanced stage, compared with unilateral PTC patients. Kim et al.(*19*) also demonstrated that CLNM in patients with PTMC was significantly associated with bilaterality. However, in the present study, there were no statistical correlations between tumor bilaterality and CLNM in PTMC.

This study showed a significant correlation between tumor multifocality and CLNM in univariate analysis (P=0.035), but multifocality was not an independent predictor of CLNM in multivariate analysis (P=0.817). Lee et al.(*20*) also found no correlation between tumor multifocality and CLNM in a retrospective study. On the other hand, several investigators have reported that multifocality influences PTMC recurrence and is an independent predictor of metastasis.(*17*) Hay et al.(*3*) also reported that both multifocality and lymph node metastasis at diagnosis increased the risk for later nodal involvement, with 11% of multifocal tumors exhibiting recurrence, compared with only 4% of unifocal tumors. However, a recent meta-analysis showed that multifocality was significantly associated with CLNM in PTMC patients, which may be because those with a total tumor diameter (TTD) more than 10 mm represent the majority of multifocal PTMC patients.(*21*)

Generally, the risk of CLNM is known to increase with tumor size. Several authors have demonstrated that PTMC tumors measuring more than 5 mm are more likely to be associated with CLNM than those measuring less than 5 mm.(*8,12,22*) The current study showed similar results. Tumor size has also been identified as a prognostic indicator in the majority of risk stratification systems for

PTC.(*23*) However, this remains controversial for PTMC. Lee et al.(*24*) observed that the long-term risks of death and tumor recurrence were similar in matched cohorts with tumor sizes >5 and <5 mm, consistent with previous reports.(*8,16,25*) Ito et al.(*26*) also observed little change in tumor size during long-term follow-up and reported that the occurrence of metastasis was infrequent. These results suggest that tumor size may be less influential for PTMC prognosis than PTC. Nevertheless, we still believe that it has value in assessing the risk of recurrence and mortality. A large-scale prospective study is required to provide reliable information and validation for the specific risk factors in PTMC, and to confirm whether tumor size plays a role as a prognostic factor. Roti et al.(*11*) and Machens et al.(*27*) also demonstrated that PTMC size greater than 5 mm was more likely to be associated with poor prognostic factors compared with PTMC size less than 5 mm.

Capsular invasion is traditionally considered to have predictive value for CLNM.(*28*) However, capsular invasion was not an independent variable in multivariate analysis (P=0.090) in our study. A number of previous studies have reported capsular invasion frequency as high as 30%.(*29*) However, capsular invasion was reported in only 3.2% of cases in this study. The difference in frequency could be caused by different diagnostic criteria. Although the diagnosis of extrathyroidal extension was based on the pathologic findings, minimal penetration of the thyroid capsule and microscopic invasion into perithyroidal tissue might not be included in the criteria.

There are certain potential limitations in the current study.

First, patients who had not undergone lateral compartment dissection or contralateral CLND were regarded as negative. Second, this was a retrospective rather than a randomized controlled study. So, we included not only patients underwent prophylactic CLND but also therapeutic CLND.

In conclusion, age less than 45 years, male sex, tumor size greater than 5 mm, and lymphovascular invasion were risk factors associated with CLNM. Meticulous perioperative evaluation for CLNM is therefore required in patients with these risk factors expect lymphovascular invasion that was pathologic finding . Our findings may help guide clinicians in the selection of candidates suitable for CLND. Further randomized controlled trial with a longer follow-up period is necessary to determine whether the studied parameters are associated with prognosis in PTMC.

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