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Prediction of central lymph node metastasis in 392 patients with cervical lymph node-negative papillary thyroid carcinoma in Eastern China

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Abstract. Central lymph node metastasis (CLNM) is common in papillary thyroid microcarcinoma (PTMC). The aim of the present study was to investigate the risk factors associated with CLNM in clinical lateral cervical lymph node-negative (cN0) PTMC in Eastern China. A total of 392 patients with confirmed PTMC by histological examination who underwent thyroidectomy and central neck lymph node dissection (CND) between May 2011 and October 2012 at the First Affiliated Hospital of Wenzhou Medical University (Wenzhou, China) were enrolled. The clinicopathological and ultrasonographic data from the patients were analyzed retrospectively. A scoring system was developed on the basis of independent predictive factors for CLNM. Male gender, age <45 years, maximum tumor diameter >5 mm, lower lobe location, multifocal carcinoma with total tumor diameter >10 mm and extracapsular spread were independent predictive factors for CLNM according to logistic regression analysis. The clinicopathological score was statistically significant, with an index point ≥2 indicating CLNM with 86.2% sensitivity and 70.4% specificity. The findings of the present study indicate that CND may be recommended to be routinely performed when the clinicopathological index point ≥2.

Introduction

Papillary thyroid microcarcinoma (PTMC) is a papillary thyroid carcinoma which is ≤1.0 cm at the greatest dimension, as defined by the World Health Organization (1). Due to the wide use of high-resolution thyroid ultrasound (US) and fine needle aspiration cytology (FNAC) under US guidance, a number of patients are diagnosed with PTMC without palpable thyroid nodules, which may explain the high incidence during previous years in Eastern China (2,3). The prognosis for PTMC patients is favorable, however, there remains a 1% disease-associated mortality rate, a 5% lymph node recurrence rate and a 2.5% distant metastasis rate (4-7). The reported incidence of lymph node metastasis (LNM) has reached 40%: The common sites of metastasis include the central compartment of the neck (8). The revised American Thyroid Association guidelines recommend that central neck lymph node dissection (CND) should be considered in patients with high-risk thyroid cancer (9). However, it remains uncertain whether CND should be routinely performed on cervical lymph node-negative (cN0) patients with PTMC. Therefore, clinicopathological and US characteristic data of cN0 PTMC patients admitted into our department was retrospectively analyzed to identify the risk factors for central LNM (CLNM). Furthermore, a scoring system for differentiating between patients with and without CLNM in Eastern China was established. Written informed consent was obtained from the patients' families and ethical approval was obtained from Wengzhou Medical University (Wengzhou, China).

Patients and methods

Patients. Between May 2011 and October 2012, 1,090 patients who were diagnosed with thyroid cancer by histological examination underwent thyroidectomy at the First Affiliated Hospital of Wengzhou Medical University (Wengzhou, China) for initial diagnosis and treatment. Among these patients, 449 (41.2%) were diagnosed with PTMC by pathology, and all the patients had preoperatively undergone US. Inclusion criteria referred to the clinical evaluation criteria of cervical lymph nodes defined by Kowalski *et al* (10). The patients matching the following conditions could be diagnosed as cN0 PTMC: i) No palpable enlarged lymph node on clinical examination, or the maximum diameter of the enlarged lymph node was <2 cm with a soft texture; ii) no visible enlarged lymph node in the imaging exam-

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ination, the maximum diameter of the enlarged lymph node was <1 cm or the maximum diameter was 1-2 cm with no central liquefaction necrosis, peripheral enhancement or disappeared fat gap adjacent to the lymph node. Using these criteria, a total of 392 patients who had undergone CND were enrolled in the present study to evaluate risk factors that may predict CLNM. The study group included 308 (78.6%) female and 84 (21.4%) male patients. The mean age at diagnosis was 47.62 [range, 18-83; standard deviation (SD), 9.77] and the average tumor size was 7.05 mm (range, 1-10 mm; SD, 1.97). All the patients were from Eastern China (the majority of patients were from Wenzhou). Table I lists the demographic and clinicopathological data of the 392 patients. Age at diagnosis, gender, tumor size, location, multifocality and bilaterality, extracapsular spread (ECS), chronic lymphocytic thyroiditis and the status of the central lymph nodes were recorded through the retrospective review of clinical data and pathological reports. The status of the central lymph nodes was diagnosed by a final pathological examination. Chronic lymphocytic thyroiditis was confirmed by serological examination or frozen biopsy with 100% sensitivity and 99.3% specificity. US was performed with Acuson Sequoia and 128XP sonographic scanners (Siemens Medical Solutions, Mountain View, CA, USA) equipped with commercially available 8-13 MHz linear probes. Real-time US was performed by experienced radiologists dedicated to thyroid imaging. US findings of patients were further categorized according to composition, echogenicity, calcifications, margin, shape and width/length. When multiple PTMCs were found in the surgical specimen, the characteristics of the largest or most dominant tumor on the preoperative US were analyzed.

Grouping. In the present study, total or almost total thyroidectomy was performed on the patients. Ipsilateral CND for unilateral cN0 PTMC patients or bilateral CND for bilateral cN0 PTMC patients was performed. According to the presence of CLNM, patients were divided into two groups: CLNM-negative (Group I) and CLNM-positive (Group II).

Statistical analysis. Statistical analysis was performed to assess the differences between groups I and II with SPSS software, version 19.0 (SPSS, Inc., Chicago, IL, USA). All statistical tests were two-sided and P<0.05 was considered to indicate a statistically significant difference. Univariate analysis with the χ^2 test was used for categorical data to analyze the statistical correlation between the factors and CLNM. Multivariate logistic regression analyses were performed to assess independent associations of CLNM with all the factors that were observed to be statistically significant by the univariate analysis. Odds ratios (ORs) with the relative 95% confidence intervals (CIs) are presented. Characteristics which were independent factors were given different points to develop a score system according to the multiple logistic regression analysis. Receiver operating characteristic (ROC) curves were used to identify the optimal point with a high sensitivity and low false-negative rate (100 - specificity).

Table I. Clinicopathological characteristics of 392 patients.

Characteristics	Value
Total number	392
Age (years)	
At diagnosis	47.62±9.77 (18-83)
<45	132 (33.7)
≥45	260 (66.3)
Gender	
Female	308 (78.6)
Male	84 (21.4)
Tumor size (mm)	7.05±1.97 (1-10)
Location	
Upper	129 (32.9)
Middle	146 (37.2)
Lower	101 (25.8)
Isthmus	16 (4.1)
Multifocality	
Unifocal	332 (84.7)
Multifocal	60 (15.3)
Tumor bilaterality	
Unilateral	340 (86.7)
Bilateral	52 (13.3)
Extracapsular spread	
Present	38 (9.7)
Absent	354 (90.3)
Chronic lymphocytic thyroiditis	
Present	85 (21.7)
Absent	307 (78.3)
Central lymph node metastasis	
Yes	159 (40.6)
No	233 (59.4)

Data are expressed as the mean ± standard deviation (range) or n (%).

Results

Among the 392 patients enrolled in this study, 308 were female and 84 were male, aged 18-83 years with a median age of 47.62 years. The mean diameter of nodules was 7.05 mm (range, 1-10 mm; SD, 1.97). A total of 159 patients (40.6%) were demonstrated to exhibit CLNM by the final pathological examination, while the other 233 patients (59.4%) did not. Table II presents the comparison of clinicopathological and US differences between CLNM-negative (Group I) and CLNM-positive (Group II) groups. Male gender, age <45 years, maximum tumor diameter >5 mm, lower lobe location and multifocal carcinoma with total tumor diameter (TTD) >10 mm were significantly correlated with the incidence of CLNM (P<0.001). ECS was significantly associated with CLNM (P=0.022). Tumor bilaterality, chronic lymphocytic thyroiditis and US characteristics did not predict CLNM in PTMC. A multivariate logistic regression analysis was performed on the factors that were revealed to be statistically significant by the univariate analysis. Male gender (OR, 5.021; P<0.001), tumor size >5 mm (OR, 4.842; P<0.001), age <45 years (OR, 3.911; P<0.001), lower lobe location (OR, 4.652; P<0.001), ECS (OR, 3.885; P=0.002) and TTD >10 mm (OR,

Table II. Clinicopathological and ultrasonographic characteristics according to central lymph node metastasis status.

Characteristics	Group I, n=233 (%)	Group II, n=159 (%)	P-value
Age (years)			<0.001[a]
<45	55 (78.5)	77 (53.5)	
≥45	178 (154.5)	82 (105.5)	
Gender			<0.001[a]
Female	202 (183.1)	106 (124.9)	
Male	31 (49.9)	53 (34.1)	
Tumor size (mm)			<0.001[a]
≤5	106 (78.5)	26 (53.5)	
>5	127 (154.5)	133 (158.5)	
≤7	140 (131.4)	81 (89.6)	0.079
>7	93 (101.6)	78 (69.4)	
Location			<0.001[a]
Upper lobe	190 (163.5)	85 (111.5)	
Lower lobe	43 (69.5)	74 (47.5)	
Multifocality			0.106
Unifocal	203 (197.3)	129 (134.7)	
Multifocal	30 (35.7)	30 (24.3)	
TTD (mm)			
≤10	28 (27.6)	17 (17.4)	0.889
>10	2 (8.9)	13 (6.1)	<0.001[a]
Tumor bilaterality			0.137
Unilateral	207 (202.1)	133 (137.9)	
Bilateral	26 (30.9)	26 (21.1)	
Extracapsular spread			0.022[a]
Present	16 (22.6)	22 (15.4)	
Absent	217 (210.4)	137 (143.6)	
Chronic lymphocytic thyroiditis			0.103
Present	44 (50.5)	41 (34.5)	
Absent	189 (182.5)	118 (124.5)	
Composition			0.222
Solid	124 (226.5)	157 (154.5)	
Cystic or mixed	9 (6.5)	2 (4.5)	
Echogenicity			0.248
Hyperchogonicy or isoechoic	227 (229.4)	159 (156.6)	
Hypoeschogenicy	6 (3.6)	0 (2.4)	
Margin			1.000
Well-defined	148 (148.0)	101 (101.0)	
Ill-defined	85 (85.0)	58 (58.0)	
Calcification			0.105
Present	138 (145.6)	107 (99.4)	
Absent	95 (87.4)	52 (59.6)	
Shape			0.363
Non-parallel	55 (58.8)	44 (40.2)	
Parallel	178 (174.2)	115 (118.8)	
Taller than wide			0.715
Yes	126 (124.2)	83 (84.8)	
No	107 (108.8)	76 (74.2)	

Group I, central lymph node metastasis-negative; Group II, central lymph node metastasis-positive. [a]Statistically significant (P<0.05). TTD, total tumor diameter.

Table III. Multivariate analysis of the associations between central lymph node metastasis and clinicopathological characteristics.

			95% confidence interval	
Characteristics	P-value	Odds ratio	Lower	Upper
Male gender	<0.001	5.021	2.735	9.215
Age (>45 years)	<0.001	3.911	2.316	6.604
Tumor size (>5 mm)	<0.001	4.842	2.765	8.479
Lower lobe	<0.001	4.652	2.707	7.992
Total tumor diameter (>10 mm)	0.016	8.553	1.486	49.226
Extracapsular spread present	0.002	3.885	1.638	9.217

Table IV. Clinicopathological index points.

Characteristic	Category	Points
Gender	Male	1
	Female	0
Age (years)	<45	1
	≥45	0
Tumor size (mm)	>5 mm	1
	≤5 mm	0
Tumor location	Upper lobe	1
	Lower lobe	0
Total tumor diameter (mm)	>10	1
	≤10	0
Extracapsular spread	Present	1
	Absent	0

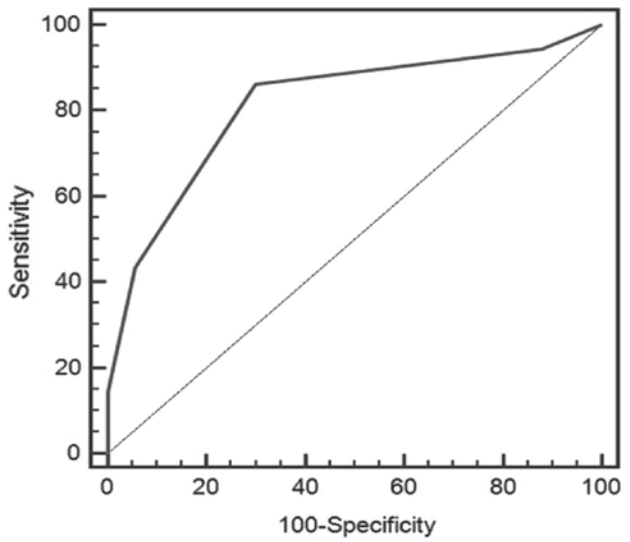

Figure 1. Receiver operating characteristic curves for CLNM. Index point ≥2 was found to be the optimal point to distinguish between patients with and without CLNM. The sensitivity and specificity were 86.2% and 70.4%, respectively. CLNM, central lymph node metastasis.

8.553; P=0.016) were identified as statistically significant independent predictive factors for CLNM (Table III). According to the multiple logistic regression analysis, the patients were scored by giving an index point to each characteristic that was significantly associated with CLNM. The index score for each characteristic is presented in Table IV. The mean clinicopathological score was 1.23±0.722 in the CLNM-positive group and 2.34±0.973 in the CLNM-negative group, which was a statistically significant difference (P<0.001). ROC curves were then used to identify that an index point ≥2 was the optimal point to distinguish between patients with and without CLNM (Fig. 1). The sensitivity and specificity reached 86.2% and 70.4%, respectively, with an area under the ROC curve of 0.816.

Discussion

Owing to the widespread use of thyroid US and US-guided FNAC, the incidence of PTMC has increased in Eastern China in previous years (2,11). Although PTMC is generally associated with an excellent prognosis, CLNM is common in PTMC patients with an incidence of 41-64% (12-17). There is no controversy in performing therapeutic neck dissection on cervical lymph node-positive PTMC patients to reduce the chance of persistence and recurrence (18), however debate remains as to whether CND should be performed on cN0 PTMC patients. A number of authors have proposed that there should be routine CND in patients with PTMC since there is evidence demonstrating that residual metastases in cervical lymph nodes represent the most common site of recurrent disease, and repeated operations may increase the incidence of operative complications, including hypoparathyroidism and damage to the laryngeal nerve (19). However, a previous study indicated that CND is not required, as the presence of CLNM is not associated with the disease-free survival rate of patients (20). The present study focused on identifying the preoperative and intraoperative predictive factors for CLNM in cN0 PTMC patients, which may aid in identifying approaches to appropriate surgical treatment for patients in Eastern China. Although the use of thyroid US for detecting CLNM is limited (20), the present study also investigated characteristics of US to identify any potential predictors.

The incidence of CLNM in the present study was 40.6% (n=159), which is consistent with previous studies (21,22). Statistical analyses performed between the CLNM-positive and -negative groups in the present study included eight clinicopathological parameters. The results demonstrated that male gender, age <45 years, maximum tumor diameter >5 mm, lower lobe location and multifocal carcinoma with

TTD >10 mm were independent predictors for CLNM from the multivariate analysis. Zeng *et al* (23) indicated that certain US characteristics (upper pole location, no well-defined margin and presence of calcifications) were predictive factors for lateral LNM in patients with PTMC in Eastern China. Few studies have reported the associations between US characteristics and CLNM. In the present study, no significance was identified for these associations, which is consistent with a previous study by Kim *et al* (24).

A number of previous studies have reported that age is not associated with CLNM in patients with PTMC (24,25). However, Wang *et al* (26) demonstrated that there is a significant difference between patients <45 years old and ≥45 years old in cN0 PTMC. The present study identified that age <45 years was significantly associated with CLNM patients. Male gender has been considered to be an important prognostic characteristic of CLNM by a number of previous studies (21,27). The present study demonstrated a significant association between male gender and CLNM, which is consistent with these previous reports. Tumor size has been previously confirmed as a prognostic feature of CLNM (20). Lee *et al* (28) demonstrated that PTMC with tumor size >7 mm had a stronger association with poor prognosis compared with those <7 mm. Lim *et al* (25) had reported that tumor size >5 mm was frequently associated with CLNM. The results of the present study demonstrated no difference between the ≤7 and >7 mm tumor size groups. However, the univariate and multivariate analyses confirmed tumor size >5 mm as an independent predictor of LNM. A number of previous studies reported the upper pole location as an independent predictive factor for lateral LNM (23,29). To the best of our knowledge, few reports have defined the statistical correlation between tumor location and CLNM in PTMC. Wang *et al* (26) proposed that the CLNM rate in the lower/middle pole group was significantly increased compared with that of the upper pole group. A study by Choi *et al* (30) demonstrated that tumors located in the upper neck had an increased risk of lateral LNM, while tumors in the lower neck had an increased risk of CLNM. Similarly, the present study determined that lower lobe location was significantly associated with CLNM in patients with cN0 PTMC. The association between tumor multifocality and CLNM remains controversial. In the present study, multifocality was not an independent predictor of CLNM, which is not consistent with previous reports (21,24). Therefore, the TTD, which was defined as the sum of the maximal diameter of each lesion, was calculated. Univariate and multivariate analyses revealed that TTD >10 mm was statistically significantly associated with CLNM in the present study, which was similar to the findings of a previous study by Zhao *et al* (31). In the present study, tumor bilaterality was not an independent predictive factor for CLNM, although this has been demonstrated to be significantly associated with CLNM in a previous study (24). ECS is an important prognostic characteristic of CLNM. ECS in patients with CLNM was significantly increased compared with that in those without CLNM in the present study, which was confirmed by certain previous reports (27,32). In the present study, coexisting chronic lymphocytic thyroiditis was found in 21.7% of patients with PTMC. Patients with chronic lymphocytic thyroiditis are considered to be more likely to exhibit thyroid carcinoma compared with patients without this condition (33,34). A previous report indicated that coexisting chronic lymphocytic thyroiditis in patients with papillary thyroid carcinoma had an inverse correlation with CLNM (35). The present study demonstrated that the frequency of CLNM was 48.2% (41/85 cases) in the chronic lymphocytic thyroiditis group, which was reduced compared with the control group. However, underlying chronic lymphocytic thyroiditis was not statistically significantly associated with CLNM.

To improve the diagnostic accuracy, a scoring system of independent predictors based on the multiple logistic regression analysis was established. The ROC curves had high predictive performance since the area under the ROC curves was 0.85 (95% CI, 0.81-0.90). Using the ROC curves, index point ≥2 was identified as the optimal cut-off point to distinguish CLNM-positive from CLNM-negative, with a sensitivity of 86.2% and a specificity of 70.4%. These results may aid surgeons to tailor the follow-up treatment of each patient accurately.

There are certain potential limitations in the current study. First, not all risk factors are included, such as lateral LNM, since only 12 patients (3.06%) enrolled in the present study underwent lateral neck dissection. Second, tumor recurrence and disease-free survival rate were not investigated. Further studies should be designed to confirm whether the scoring system is useful for treatment outcome.

In conclusion, this scoring system for the prediction of CLNM may be a practical and convenient diagnostic approach for cN0 patients with PTMC in Eastern China. Patients with an index point <2 may be considered as CLNM-negative. For patients with index point ≥2, the present study indicates that a CND may be routinely performed.

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