

Risk Factor Analysis for Central Lymph Node Metastasis in Papillary Thyroid Microcarcinoma

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Purpose: Although the prognosis of papillary thyroid microcarcinoma (PTMC) is excellent, cervical lymph node metastasis (CLNM) is commonly observed in PTMC. This study aimed to investigate the incidence and risk factors for CLNM in PTMC.

Patients and Methods: Altogether, 687 patients with PTMC who initially underwent unilateral thyroidectomy with unilateral central lymph node dissection or bilateral thyroidectomy with bilateral central lymph node dissection between January 2014 and June 2018 at our hospital were included. The patients were divided into two groups: PTMC with CLNM and PTMC with no CLNM. The clinicopathologic characteristics and ultrasound features were compared between the groups. Univariate and multivariate logistic regression analyses were used to identify the risk factors for CLNM.

Results: CLNM was observed in 121/687 (17.6%) patients with PTMC. PTMC patients aged <55 years exhibited a greater incidence of CLNM (87.6% vs 12.4%) than those aged ≥55 years. PTMC patients with CLNM were more likely to have capsular extension (24.0% vs 15.4%) and extension to the adjacent structures (9.9% vs 4.2%). Patients with microcalcification on ultrasound images were more likely to have CLNM (66.1% vs 47.9%). Multivariate logistic regression analysis revealed that microcalcification (odds ratio [OR]: 2.066, 95% confidence interval [CI]: 1.361–3.135, $P < 0.001$), age <55 years (OR: 2.341, 95% CI: 1.309–4.187, $P = 0.004$), capsular invasion (OR: 1.772, 95% CI: 1.082–2.879, $P = 0.023$), and invasion of the adjacent tissues (OR: 2.872, 95% CI: 1.355–4.187, $P = 0.004$) were significant risk factors for CLNM.

Conclusion: Microcalcification, age <55 years, capsular invasion, and invasion of the adjacent tissues were significant risk factors for CLNM in PTMC.

Keywords: risk factors, papillary thyroid microcarcinoma, microcalcification, age, invasion

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Introduction

Papillary thyroid microcarcinoma (PTMC) is defined as a malignant thyroid tumor sized ≤1 cm.¹ PTMC is a subtype of papillary thyroid cancer (PTC) and accounts for approximately 30–50% of the PTCs.² In recent years, the prevalence of thyroid microcarcinoma has increased rapidly, mainly due to the detection of thyroid nodules using advanced ultrasound (US).^{3,4} It is well known that most of the PTMCs are indolent with excellent prognosis and the long-term survival rate is over 99%.⁵ However, central lymph node metastasis (CLNM) is common and may be observed in 21.4–60% of the PTMCs.^{2,6–10} CLNM might be the main risk factor for tumor recurrence.¹¹ Although prophylactic central lymph node dissection can reduce tumor recurrence rates and reoperation-related complications, it can result in surgical complications such as permanent hypocalcemia and recurrent laryngeal nerve injury.^{12,13} Therefore, the decision

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to perform prophylactic central lymph node dissection for PTMC is still controversial. Although several previous studies have assessed the risk factors for CLNM in PTMC, these factors remain unclear to date. It is necessary to analyze the clinicopathological characteristics and US characteristics of PTMC patients to determine the independent risk factors for CLNM in thyroid microcarcinoma and to formulate a relatively reasonable surgical plan.

Materials and Methods

This present study was approved by the Ethics Committee of Shanghai Sixth People's Hospital and all patients provided informed consent to participate in this study.

The clinicopathological characteristics of PTMC patients included age, sex, tumor size, presence of chronic thyroiditis, degree of tumor invasion, surgical methods, single or multifocal tumor, and dissected lymph nodes. According to the eighth edition of the Oncology Manual, patients were classified as ≥ 55 years of age and < 55 years of age. For unifocal tumors, the tumor size was calculated as the largest diameter of the tumor. For multifocal tumors, the tumor size was calculated as the largest diameter of the largest mass. According to the postoperative paraffin section pathological report, tumor invasion was classified as invasion within the thyroid capsule, invasion into the capsule, and tumor extension to the adjacent tissues outside the capsule. Tumor within the thyroid capsule refers to a mass within the gland and not extending to the capsule. Tumor invading the capsule refers to a mass that is close to the surface of the thyroid and invades the capsule. Tumor extending to the adjacent tissues outside the capsule refers to a mass that breaks through the thyroid capsule and invades tissues such as fat and muscles outside the gland. Chronic thyroiditis has been studied as a risk factor or a protective factor for CLNM.^{14,15} For patients with unilateral PTC, unilateral thyroidectomy was performed with unilateral central lymph node dissection. For patients with bilateral PTC or PTC arising from the isthmus, bilateral thyroidectomy and bilateral central lymph node dissection were performed. US features considered in this study included tumor shape, tumor boundary, microcalcification, and suspicion of CLNM. The shape of the mass was classified as regular or irregular and the boundary of the mass was classified as clear or unclear. Microcalcifications were defined as punctate hyperechoic lesions within the tumor with a size ≤ 2 mm. Neck US examinations were performed at our hospital 1 week before the surgery. Patients with a tumor size > 1 cm were excluded.

The chi-squared test was used to analyze the differences in the clinical variables between patients with CLNM and those without CLNM. Univariate and multivariate logistic regression analyses were used to verify the risk factors for thyroid microcarcinoma. Variables with *P*-values below 0.05 in the univariate logistic regression analysis were included in the multivariate logistic regression analysis. The programming software R (version 4.0.5, <https://www.r-project.org>) (the R foundation, Vienna, Austria) was used for statistical analyses.

Results

Clinical Characteristics

Altogether, 687 patients with PTMC were included in the study. CLNM was observed in 121 (17.6%) patients with PTMC, while 566 (82.4%) PTMC patients did not exhibit CLNM. The study included 164 (23.9%) men and 523 (76.1%) women. Altogether, 528 (76.9%) patients aged < 55 years and 159 (23.1%) patients aged ≥ 55 years were included in our investigation. Total thyroidectomy with bilateral central lymph node dissection was performed in 215 (31.3%) PTMC patients, while 472 (68.7%) underwent lobectomy and isthmusectomy with ipsilateral bilateral central lymph node dissection.

Ultrasound Features

Altogether, 276 (40.2%) and 411 (59.8%) patients had tumors with irregular and regular shapes, respectively. Tumors with unclear margins were observed in 385 (56.0%) patients, while 302 patients (44.0%) had tumors with clear margins. Microcalcifications within the tumor were observed in 351 (51.1%) patients, while 336 (48.9%) patients had tumors without microcalcifications. CLNM was suspected on US imaging in 41 patients (6.0%).

Pathological Features

Tumor size was ≥ 5 mm in 503 (73.2%) patients, while 184 (26.8%) patients had tumor size < 5 mm. Altogether, 84 (12.2%) PTMC patients had multifocal tumors. Tumors were confined to the capsule in 535 (77.9%) patients, extension to the capsule was observed in 116 (16.9%) patients, and extension to the adjacent structures was observed in 36 (5.2%) patients. The detailed information is presented in Table 1.

Statistical Analysis

Analysis with chi-squared test showed significant differences in patient age, tumor extension, and the presence or

Table 1 Detailed Information of All PTMC Patients

	Overall
n	687
CLNM, n (%)	
Yes	121 (17.6)
No	566 (82.4)
Sex, n (%)	
Male	164 (23.9)
Female	523 (76.1)
Irregular shape, n (%)	
Yes	276 (40.2)
No	411 (59.8)
Unclear margin, n (%)	
Yes	385 (56.0)
No	302 (44.0)
Microcalcification, n (%)	
Yes	351 (51.1)
No	336 (48.9)
Suspected CLNM, n (%)	
Present	41 (6.0)
Absent	646 (94.0)
Age, n (%)	
<55 years	528 (76.9)
≥55 years	159 (23.1)
Multifocal, n (%)	
Present	84 (12.2)
Absent	603 (87.8)
Size, n (%)	
≥5mm	503 (73.2)
< 5mm	184 (26.8)
CLT, n (%)	
Present	109 (15.9)
Absent	578 (84.1)
Tumor extension, n (%)	
Confined into the capsule	535 (77.9)
Extension to the capsule	116 (16.9)
Extension to adjacent structures	36 (5.2)
Surgical resection, n (%)	
Total thyroidectomy with bilateral CLND	215 (31.3)
Lobectomy plus isthmusectomy with ipsilateral CLND	472 (68.7)
No. of the harvested lymph nodes (mean (SD))	3.91 (1.32)

Abbreviations: CLNM, central lymph node metastasis; CLT, chronic lymphatic thyroiditis; CLND, central lymph node dissection; PTMC, papillary thyroid microcarcinoma.

absence of microcalcification ($P<0.05$) between the groups. Sex, tumor boundary, and other variables did not show significant differences.

As shown in Table 2, PTMC patients with CLNM were more likely to have an extension to the capsule (24.0% vs 15.4%) or extension to the adjacent structures (9.9% vs 4.2%) compared to those without CLNM. Patients with microcalcification on US imaging were more likely to

Table 2 Comparison of Information Between PTMC Patients with NCLNM and PTMC with CLNM

Factors	NCLNM	CLNM	P value
n	566 (82.4)	121 (17.6)	
Sex, n (%)			
Male	130 (23.0)	34 (28.1)	0.278
Female	436 (77.0)	87 (71.9)	
Irregular shape, n (%)			
Yes	220 (38.9)	56 (46.3)	0.159
No	346 (61.1)	65 (53.7)	
Unclear margin, n (%)			
Yes	312 (55.1)	73 (60.3)	0.344
No	254 (44.9)	48 (39.7)	
Microcalcification, n (%)			
Yes	271 (47.9)	80 (66.1)	<0.001
No	295 (52.1)	41 (33.9)	
Suspected CLNM, n (%)			
Present	31 (5.5)	10 (8.3)	0.335
Absent	535 (94.5)	111 (91.7)	
Age, n (%)			
<55 years	422 (74.6)	106 (87.6)	0.003
≥55 years	144 (25.4)	15 (12.4)	
Multifocal, n (%)			
Present	70 (12.4)	14 (11.6)	0.928
Absent	496 (87.6)	107 (88.4)	
CLT, n (%)			
Present	97 (17.1)	12 (9.9)	0.066
Absent	469 (82.9)	109 (90.1)	
Tumor extension, n (%)			
Confined into the capsule	455 (80.4)	80 (66.1)	0.001
Extension to the capsule	87 (15.4)	29 (24.0)	
Extension to adjacent structures	24 (4.2)	12 (9.9)	
Size, n (%)			
≥5mm	410 (72.4)	93 (76.9)	0.377
< 5mm	156 (27.6)	28 (23.1)	
Surgical resection, n (%)			
Total thyroidectomy with bilateral CLND	181 (32.0)	34 (28.1)	0.467
Lobectomy plus isthmusectomy with ipsilateral CLND	385 (68.0)	87 (71.9)	

Abbreviations: CLNM, central lymph node metastasis; NCLNM, non central lymph node metastasis; CLT, chronic lymphatic thyroiditis; PTMC, papillary thyroid microcarcinoma.

have CLNM (66.1% vs 47.9%) compared to those without microcalcification. Univariate analysis showed that microcalcification, age, and tumor invasion were significantly correlated with CLNM ($P < 0.05$) as shown in Table 3.

Table 3 Univariate Analysis of Variables Related to Central Lymph Node Metastasis (CLNM)

Characteristics	OR	95% CI	P value
Sex			
Male	1.311	0.842–2.04	0.2304
Female	Reference		
Age			
<55 years	2.411	1.36–4.276	0.0026
≥55 years	Reference		
Size			
≥5mm	1.264	0.797–2.004	0.3196
< 5mm	Reference		
Irregular shape			
Yes	1.355	0.913–2.012	0.132
No	Reference		
Unclear margin			
Yes	1.238	0.83–1.847	0.2954
No	Reference		
Microcalcification			
Yes	2.124	1.408–3.204	0.0003
No	Reference		
Suspected CLNM			
Present	1.555	0.741–3.264	0.2434
Absent	Reference		
Multifocal			
Present	0.837	0.487–1.437	0.5176
Absent	Reference		
CLT			
Present	0.532	0.282–1.004	0.0516
Absent	Reference		
Tumor extension			
Confined into the capsule	Reference		
Extension to the capsule	1.896	1.17–3.072	0.0094
Extension to adjacent structures	2.844	1.367–5.916	0.0052
Surgical resection			
Total thyroidectomy with bilateral CLND	0.831	0.539–1.283	0.4039
Lobectomy plus isthmusectomy with ipsilateral CLND	Reference		

Abbreviations: CLNM, central lymph node metastasis; CLT, chronic lymphatic thyroiditis; CLND, central lymph node dissection; PTMC, papillary thyroid microcarcinoma; OR, odds ratio; CI, confidence interval.

Table 4 Multivariate Analysis of Variables Related to Central Lymph Node Metastasis (CLNM)

	OR	95% CI	P value
Microcalcification			
Yes	2.066	1.361–3.135	<0.001
No	Reference		
Tumor extension			
Confined into the capsule	Reference		
Extension to the capsule	1.772	1.083–2.897	0.023
Extension to adjacent structures	2.872	1.355–6.089	0.006
Age			
<55 years	2.341	1.309–4.187	0.004
≥55 years	Reference		

Abbreviations: OR, odds ratio; CI, confidence interval.

Multivariate analysis revealed that microcalcification (odds ratio [OR]: 2.066, 95% confidence interval [CI]: 1.361–3.135, $P < 0.001$), age <55 years (OR: 2.341, 95% CI: 1.309–4.187, $P = 0.004$), extension to the capsule (OR: 1.772, 95% CI: 1.083–2.897, $P = 0.023$) and extension to the adjacent structures (OR: 2.287, 95% CI: 1.355–6.089, $P = 0.006$) were significantly associated with CLNM. The detailed information is presented in Table 4.

Discussion

PTMC is described as a malignant thyroid tumor with a maximum diameter ≤ 1 cm. In recent years, the prevalence of PTMC has increased rapidly due to advancements in detection technologies such as the US.^{16,17} It is well known that PTMC is an indolent cancer with an excellent prognosis. The 10-year disease-free survival rate is over 96%.⁵ However, CLNM is commonly observed in PTMC. According to a previous investigation, approximately 35.5% of the PTMCs have CLNM.⁹ The central area is the first station of CLNM. Moreover, metastasis to the central area is the most common form of CLNM.^{8–10,18} However, the decision regarding the implementation of preventive cervical lymph node dissection is still controversial. Several researchers believed that performance of routine central neck dissection could attain a less recurrence, better outcomes, reduced postoperative thyroglobulin levels and a lower morbidity rate related to initial operation.^{19,20} Nevertheless, others thought that more aggressive process could increase the threat of surgical complication such as permanent hypocalcemia, hypoparathyroidism and recurrent laryngeal nerve paralysis.^{21,22} Therefore, the present study retrospectively analyzed the

clinicopathological and US characteristics of 678 patients with PTMC to analyze the risk factors associated with CLNM in a single-institution. We observed that the rate of CLNM in thyroid microcarcinoma was 17.6%. In a previous study, the incidence of CLNM in PTMC ranged from 24.1% to 64.1%.^{2,6–10} The high incidence of CLNM indicates that it is relatively reasonable to perform prophylactic central lymph node dissection in PTMC patients.

The results of the present study suggested that patients aged <55 years were more likely to develop CLNM than patients aged ≥55 years, indicating that younger patients should be monitored more carefully, and clinicians should consider prophylactic central lymph dissection in younger patients. Several previous studies have shown that age is closely related to CLNM in patients with PTMC. Liu et al demonstrated that age <45 years was significantly associated with CLNM.²³ The age cut-off of 45 years has been adopted in the commonly used staging system for differentiated thyroid cancer for many years. However, Nixon et al identified that a cut-off of 55 years would enhance the precision of the staging system and would suitably avoid overstaging and overtreatment of low-risk patients.²⁴ Therefore, the age cut-off was changed from 45 years to 55 years in the eighth edition of the American Joint Committee on Cancer (AJCC)/The Union for International Cancer Control staging system. Currently, it is not clear whether a cut-off age of 45 years or 55 years would be suitable for predicting CLNM in PTMC patients. However, our findings confirmed that patients under 55 years of age had a higher incidence of CLNM than those over 55 years of age.

We observed that microcalcification inside the tumor on US imaging was also a dependent risk factor for CLNM in PTMC patients. Johannessen and Sobrinho-Simoes demonstrated the pathogenesis of calcification in the thyroid for the first time. A probable reason for microcalcification is that the rapid proliferation of cancer cells may lead to proliferation and mixed necrosis of cancer tissues, leading to calcium deposition and calcification. Necrotic calcification caused by tumor thrombus is another probable reason.²⁵ Thus, microcalcification is due to the proliferation of blood vessels and fibrous tissue, which reflects the rapid growth of the mass to a certain extent. Oh et al confirmed that PTMC patients with presence of microcalcification on US imaging exhibited a higher rate of lymph node metastasis, which was consistent with our results.²⁶ Therefore, clinicians should pay careful attention to the

possibility of CLNM in PTMC patients with microcalcification on US imaging.

We observed that tumor extension was significantly associated with CLNM. When compared with tumors confined to the capsule, tumors extending to the capsule or the adjacent tissues exhibited a higher probability of CLNM. Gui et al demonstrated that extrathyroidal extension was associated with CLNM in PTMC.²⁷ Moreover, extrathyroidal extension was emphasized as an unfavorable prognostic factor in the eighth edition of the AJCC staging manual. Therefore, PTMC patients with tumor extension to the capsule or the adjacent tissues including the strap muscles, recurrent laryngeal nerves, larynx, trachea, esophagus, veins, and carotid artery were more likely to develop CLNM.

Our study has several limitations. The existence of data bias and deviation due to the retrospective study design was unavoidable. Central lymph node dissection was performed in all patients with PTMC, which might have resulted in medical overtreatment. The relevant data from the present investigation was limited to a single institution. Data from multiple institutions are needed to study the risk factors for CLNM in PTMC.

Conclusion

We observed that microcalcification on US imaging, age <55 years, and extension to the capsule or the adjacent tissues were significantly associated with CLNM. These findings could be beneficial for the clinicians in confirming CLNM in PTMC patients.

Abbreviations

PTMC, papillary thyroid microcarcinoma; PTC, papillary thyroid carcinoma; US, ultrasound; CLNM, central lymph node metastasis; AJCC, American Joint Committee on Cancer; OR, odds ratio; CI, confidence interval.

Code Availability

The code used or analyzed during the current study are available from the corresponding author on reasonable request.

Data Sharing Statement

The datasets used or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics Statement

This study was conducted with the approval of the Ethics Committee of Shanghai Jiao Tong University Affiliated Sixth People's Hospital and in accordance with the declaration of Helsinki. Written informed consent was obtained from all participants.

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Disclosure

The authors report no conflicts of interest.

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