

Risk factors for lymph node metastasis (LNM) in patients with papillary thyroid microcarcinoma (PTMC): role of preoperative ultrasound

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Abstract

Objective: This study aimed to investigate the risk factors and clinical value of lymph node metastasis (LNM) and missed central lymph node metastasis (CLNM) using preoperative ultrasound (US) in patients with papillary thyroid microcarcinoma (PTMC).

Methods: This retrospective study included 521 patients who underwent thyroidectomy for confirmed PTMC based on a final histological examination between January 2014 and June 2015. Based on the presence of LNM, 521 cases were divided into two groups: metastasis (218) and non-metastasis (303). Univariate and multivariate logistic regression analyses were used to analyse the US and clinical characteristics of the primary tumour.

Results: We defined LNM based on the tumour diameter with an optimal critical value of 0.55 cm using ROC analysis with a sensitivity of 65.6% and specificity of 59.6%. We defined US-missed CLNM based on the optimal critical value of 0.65 cm using diagnostic ROC analysis with a sensitivity of 66.0% and specificity of 73.0%. The odds ratios of significant factors with LNM by US were 10.3 (95% confidence interval [95% CI], 6.2–17.0), 5.3 (95% CI, 3.3–8.7), 2.7 (95% CI, 1.1–6.5), 4.3 (95% CI, 1.7–10.5), 2.5 (95% CI, 1.5–4.1), and 2.7 (95% CI, 1.7–4.4) for extrathyroidal invasion, blood flow, multifocality, tumour diameter greater than 0.55 cm, male sex, and age younger than 47 years, respectively.

Conclusions: US characteristics, such as extrathyroidal invasion, blood flow, tumour diameter, sex, and age, may improve the efficacy of predicting LNM and facilitating diagnosis of PTMC. Furthermore, tumour invasion to the extracapsular thyroid and a diameter greater than 0.65 cm indicate CLNM.

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Keywords

Papillary thyroid microcarcinoma, lymph node metastasis, central lymph node metastasis, ultrasound

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Abbreviations

LNM	Lymph node metastasis
CLNM	Central lymph node metastasis
PTMC	Papillary thyroid microcarcinoma
PTC	Papillary thyroid carcinoma
ROC	Receiver-operating characteristic
FNAC	Fine-needle aspiration cytology
LND	Lymph node dissection
CCND	Central neck lymph node dissection

Introduction

The increased detection of thyroid nodules of papillary thyroid carcinoma (PTC) in recent years has been attributed to the widespread use of high-resolution thyroid ultrasound (US) and fine-needle aspiration cytology (FNAC) under US guidance. PTC is the most common histological type of differentiated thyroid cancer, and is characterized by early spread to regional lymph nodes and extracapsular invasion. However, PTC has a highly favourable prognosis, with a low incidence of distant metastasis and mortality.^{1,2} Papillary thyroid carcinomas smaller than 1 cm at the greatest dimension are classified as papillary thyroid microcarcinoma (PTMC) according to the World Health Organization classification system for thyroid tumours.³ The role of surgery for PTC is controversial.^{4,5} The revised American Thyroid Association (ATA) guidelines recommend that central neck lymph node dissection (CCND) may be considered in patients with high-risk thyroid cancer.⁶ However, there is no evidence that prophylactic CCND improves loco-regional control or disease-specific survival,

particularly in PTMC. Therefore, the efficacy of prophylactic CCND in patients with PTMC is controversial. High-resolution US shows lymph node metastasis (LNM) and the findings affect the extent of surgery. The accuracy of preoperative US in early diagnosis of LNM is often limited, despite the high positive detection rate.⁷

Although, the detection of PTC has increased in the past few years, the incidence of distant metastasis and mortality has not increased. PTMC without cervical metastasis has a reported risk of mortality of < 1%, loco-regional recurrence rate of 2% to 6%, and distant recurrence rate of 1% to 2%.⁸ Some researchers question the value of early detection and treatment of PTMC. The 2015 ATA guidelines⁸ no longer recommend a biopsy for thyroid nodules less than 1 cm, even if US results are suspicious, without high-risk features, such as cervical adenopathy or extrathyroidal invasion. Therefore, prediction of LNM using preoperative US is of great clinical significance, especially for CLNM. If there are any suspicious characteristics of LNM, FNAC and further surgery should be performed. Our retrospective study aimed to investigate the US and clinical characteristics of PTMC that was confirmed by pathological diagnosis on frozen sections. Our findings could provide more guidance and help in management by improving prediction of LNM.

Materials and methods**Patients**

This study was approved by the Institutional Review Board of the Affiliated Hospital of

Qingdao University. All of the patients signed informed consent. Between January 2014 and June 2015, a total of 956 patients were pathologically diagnosed with thyroid cancer based on frozen sections at the Affiliated Hospital of Qingdao University, including 521 patients with PTMC. A retrospective review of US features was also conducted.

Instruments

US was performed with the GE LOGIQ E8, Siemens 2000, equipped with a commercially available 6 to 15-MHz linear array transducer. Board-certified radiologists with more than 5 years of experience in thyroid imaging performed US twice (including preliminary and preoperative locations). All of the patients underwent surgery after a diagnosis of papillary carcinoma based on fine-needle aspiration.

US and clinical characteristics

Various US prognostic factors, such as tumour size, shape, composition, blood flow, calcification, extrathyroidal extension, multifocality, and coexistence of chronic lymphocytic thyroiditis or nodular goiter were observed and recorded. After PTMC was confirmed surgically, the largest nodule was analysed. The internal echo of composition of the tumour was divided into solid, cystic, and solid mixed. Microcalcification was defined as coexistence of microcalcification or thick microcalcification. Absence of calcification was ascertained by nodules without calcification and only coarse calcification. An irregular shape was defined as burrs and a lobulated aspect ratio greater than 1. Extracapsular invasion was defined by tumour contact greater than 25% with the adjacent capsule.⁹

Using ROC curves, we identified the best point with high sensitivity and a low false-negative rate (1-specificity).

Surgery and pathology

In our hospital, the extent of thyroid surgery is determined according to the guidelines issued by the ATA.⁷ Total and near-total thyroidectomy with bilateral CCND was performed in patients with multiple, bilateral tumours, extrathyroidal invasion, LNM upon preoperative evaluation or intraoperative findings, first-degree familial history of thyroid cancer, or a history of head or neck radiotherapy. Patients with a single intrathyroidal lesion (≤ 1 cm), without evidence of LNM by US, without a personal history of radiation therapy to the head and neck, and without a family history of thyroid cancer, were treated with hemithyroidectomy combined with prophylactic ipsilateral CCND. The present study included 283 (54.3%) patients undergoing total thyroidectomy with bilateral CCND and 227 (43.6%) treated with hemithyroidectomy with ipsilateral CCND. Before surgery, 21 patients were diagnosed with preoperative US for suspected metastatic lymph nodes in the lateral compartment, which was proven to be negative in four patients.

Statistical analysis

The predicted tumour size in LNM and US-missed CLNM of PTMC was measured using receiver-operating characteristic (ROC) curves. Statistical analysis was performed with SPSS (version 17.0). Univariate analysis with the χ^2 test and Fisher's exact test was used to analyse the statistical correlation between risk factors and LNM, and missed CLNM of PTMC. Multivariate logistic regression analysis was performed to identify the multivariate correlates of US factors with LNM and missed CLNM of PTMC. Results are shown as odds ratios (ORs) with 95% confidence intervals (CIs). $P < 0.05$ was considered statistically significant.

Results

LNM was present in 218 (41.8%) patients, including 149 (68.3 %) who had LNM missed on US and 69 (31.7%) (of whom 21 had lateral LNM) who had LNM detected. The median age was 42 years. We defined LNM by the optimal critical value of the tumour diameter (0.55 cm) using ROC analysis, with a sensitivity of 65.6% and a specificity of 59.6% (Figure 1). We defined ultrasound-missed CLNM by the optimal critical value of the tumour diameter (0.65 cm) using ROC analysis, with a sensitivity of 66.0% and a specificity of 73.0% (Figure 2).

Univariate analysis and multivariate logistic regression analysis of PTMC with LNM

Univariate analysis showed that patients with PTMC and LNM were significantly

associated with tumour characteristics of microcalcification, extrathyroidal invasion, an irregular shape, blood flow, coexistence of nodular goiter, multifocality, and a diameter greater than 0.55 cm, male sex, and age younger than 47 years (Table 1).

Significant results that were obtained in univariate analysis were subjected to multivariate logistic regression analysis. Tumour characteristics of extrathyroidal invasion, blood flow, multifocality, and a diameter greater than 0.55 cm, male sex, and age younger than 47 years were predictive factors for LNM in multivariate analysis. The odds ratios of these significant factors with LNM by US were 10.3 (95% CI, 6.2–17.0), 5.3 (95% CI, 3.3–8.7), 2.7 (95% CI, 1.1–6.5), 4.3 (95% CI, 1.7–10.5), 2.5 (95% CI, 1.5–4.1), and 2.7 (95% CI, 1.7–4.4), respectively (Table 1).

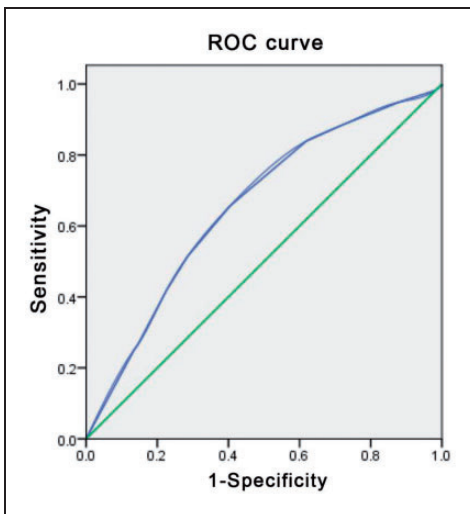


Figure 1. Receiver-operating characteristics (ROC) curve analysis for lymph node metastasis (LNM)

An index point ≥ 2 was found to be the optimal point to distinguish between PTMC with and without LNM. The sensitivity and specificity were 65.6% and 59.6%, respectively, with an area under the ROC curve of 0.655

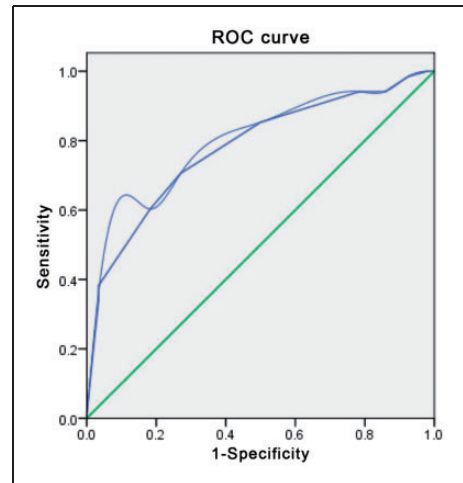


Figure 2. Receiver-operating characteristics (ROC) curve analysis for cervical lymph node metastasis (CLNM) missed by US

An index point ≥ 2 was found to be the optimal point to distinguish between PTMC with and without CLNM. The sensitivity and specificity were 66.0% and 73.0%, respectively, with an area under the ROC curve of 0.770.

Table 1. Univariate and multivariate analyses of LNM and ultrasonographic and clinical characteristics of patients with PTMC.

Ultrasound and clinical characteristics	Points	Total (n = 521)	LNM		Univariate analysis		Multivariate logistic regression analysis		95% Confidence interval	
			(+)	(-)	χ^2	P value	P value	Odds ratio	Lower	Upper
Primary tumour microcalcification										
Present	1	443	152	291	68.97	0.000	0.122	1.4	0.9	2.4
Absent	0	78	66	12						
Extrathyroidal Invasion										
Present	1	387	124	263	59.34	0.000	0.000	10.3	6.2	17.0
Absent	0	134	94	40						
Defined										
Well-defined	1	19	8	11	5.59×10^{-4}	1				
Ill-defined	0	502	210	292						
Shape										
Irregular	1	447	206	241	23.28	0.000	0.139	0.6	0.3	1.2
Regular	0	74	12	62						
Blood flow										
Absent	1	212	111	101	16.24	0.000	0.000	5.3	3.3	8.7
Present	0	309	107	202						
Coexisting lymphocytic thyroiditis										
Present	1	67	24	43	1.15	0.750				
Absent	0	454	194	260						
Coexisting nodular goiter										
Present	1	264	93	171	9.62	0.000	0.978	1.0	0.6	1.6
Absent	0	257	125	132						
Composition										
Cystic and solid mixed	1	4	1	3	9.0×10^{-4}	1				
Solid	0	517	217	300						
Multifocality										
Present	1	46	28	18	7.5	0.006	0.019	2.8	1.1	6.5
Absent	0	475	190	285						
Age (y)										
<47	1	218	60	158	31.59	0.000	0.000	0.4	0.2	0.6
>47	0	303	158	145						
Sex										
Female	1	381	134	247	25.9	0.000	0.003	0.5	0.3	0.8
Male	0	140	84	56						
Tumour size										
>0.55	1	422	131	145	16.94	0.000	0.002	4.3	1.7	10.5
<0.55	0	89	87	158						

Univariate analysis and multivariate logistic regression analysis of CLNM missed by US

In univariate analysis, unifocal lesions without calcification or extrathyroidal invasion measuring less than 0.65 cm in diameter were significantly independently correlated with CLNM missed by US (Table 2).

Significant results that were obtained in univariate analysis were subjected to multivariate logistic regression analysis. Tumours without extracapsular invasion and measuring less than 0.65 cm in diameter were independent predictive factors for missed CLNM by US in multivariate analysis. A tumour diameter less than 0.65 cm was a critical factor (Table 2).

Discussion

PTMC is defined by the World Health Organization as a tumour measuring 1.0 cm or less in diameter.⁴ Although PTMC is generally associated with an excellent prognosis, LNM, extrathyroidal invasion, and distant metastasis are common in patients with PTMC compared with those with PTM. Despite the small size and accidental discovery, the incidence of LNM in patients with PTMC ranges from 4% to 65%, with a loco-regional recurrence rate of up to 20%.^{10–12} Pathological studies have shown similar biological behaviour in terms of BRAF^{V600E}, frequency of mutation, invasiveness, patients' age, and sex.¹³ However, excessive surgical therapy may increase the risks and complications postoperatively. Therefore, preoperative US is invaluable for predicting LNM in patients with PTMC, to serve as a reference and guideline for surgery.

Several factors affect the risk of LNM in patients with PTCM. In the present study, the incidence of LNM increased to 42% (218/521), which is consistent with previous studies.^{14,15} LNM was significantly associated with independent factors, such as

age younger than 47 years, male sex, and the tumour characteristics of extrathyroidal invasion, blood flow, presence of microcalcification, and multifocality. Zhang et al.¹⁴ showed that male sex, age less than 45 years, tumour size larger than 0.6 cm, extracapsular invasion, and multifocality were associated with LNM, similar to our study. Lee et al.¹⁵ reported that LNM mainly occurred in patients with a primary tumour diameter exceeding 7 mm. Kim et al.¹⁶ showed that a threshold of 5 mm for the tumour diameter was significant. We also investigated the tumour diameter by ROC curve analysis, with an optimal cutoff of 0.55 cm, and showed a sensitivity and specificity of 65.6% and 59.6%, respectively. Univariate and multivariate logistic regression analyses showed that a primary tumour size greater than 0.55 cm on US was associated with CLNM (OR 4.3, 95% CI 1.7–10.5). The risk of LNM is known to increase with tumour size. In our study, univariate and multivariate logistic regression analyses showed that extrathyroidal extension was an independent factor for LNM. This finding may be attributed to easy dissemination of cancer cells to other sites by the destroyed capsule. LNM was found in 77% of patients with extrathyroidal extension in our study, consistent with previous studies.¹⁷ Therefore, we focussed on PTMC, which destroyed the thyroid capsule. In the present study, multifocality ($P=0.027$, OR = 2.1) was an independent predictor of LNM, as shown by other studies.^{14,21} The left and right lobes of the thyroid are connected by the lymphatic duct,¹⁸ facilitating metastasis via lymphatic spread. Tumour blood vessels are also an independent factor for LNM. Blood flow may feed growth and spread of cancer cells. The present study showed significant associations between male sex ($P=0.003<0.05$, OR = 0.5) and age younger than 47 years ($P=0.000$, OR = 0.4) and LNM, which is consistent with previous reports.^{19,20}

Table 2. Univariate and multivariate analyses of missed CLNM by US and US and clinical characteristics of patients with PTMC.

Ultrasound and clinical characteristics	Points	Total (n=197)	Central LNM		Univariate analysis		Multivariate logistic regression analysis		95% Confidence interval	
			(+)	(-)	χ^2	P value	P value	Odds ratio	Lower	Upper
Primary tumour microcalcification										
Present	1	132	41	91	9.7	0.000	0.163	2.0	0.8	5.4
Absent	0	65	7	58						
Extrathyroidal invasion										
Present	1	53	27	26	27.7	0.000	0.000	9.6	4.3	21.6
Absent	0	144	21	123						
Defined										
Well-defined	1	8	2	6	1.8×10^{-3}	1				
Ill-defined	0	189	46	143						
Shape										
Irregular	1	162	39	123	0.04	1				
Regular	0	35	9	26						
Blood flow										
Absent	1	116	24	92	2.07	1				
Present	0	81	24	57						
Coexisting lymphocytic thyroiditis										
Present	1	25	5	20	0.29	1				
Absent	0	172	43	129						
Coexisting nodular goiter										
Present	1	88	23	65	2.62	1				
Absent	0	109	25	84						
Composition										
Cystic and solid mixed	1	1	1	0	3.1	1				
Solid	0	196	47	149						
Multifocality										
Present	1	24	4	20	5.3	0.00	0.167	0.4	0.1	1.5
Absent	0	173	44	129						
Age (y)										
<47	1	80	17	63	1.83	1				
>47	0	117	31	86						
Sex										
Female	1	75	17	58	0.71	1				
Male	0	122	31	91						
Tumour size										
>0.55	1	164	32	41	7.21	0.005	0.041	5.0	1.1	23.7
<0.55	0	33	16	108						

Some studies have reported that ill-defined tumours and microcalcification are associated with LNM in patients with PTMC.⁸ However, a few studies reported that tumour composition, microcalcification, definition, and shape were not associated with LNM.²¹ In the current study, these factors were analysed. Our findings suggested that although microcalcification, ill-defined tumours, and coexisting nodular goiter were risk factors in univariate analyses, they were not significant when adjusted for other factors in multivariate analysis. A previous report showed that coexisting lymphocytic thyroiditis in patients with PTMC was correlated with LNM.^{22,23} However, So et al.¹⁹ reported that 24.9% of 551 patients with PTMC had lymphocytic thyroiditis and there was no association between lymphocytic thyroiditis and LNM. Kim et al.²² showed that lymphocytic thyroiditis did not affect the frequency of LNM in all PTMC cases. The present study showed that the frequency of LNM was 35% (24/69 cases) in the lymphocytic thyroiditis group, which was lower compared with the control group. However, underlying lymphocytic thyroiditis was not significantly associated with CLNM.

The widespread use of US and US-FNAB has resulted in an increased number of preoperative diagnoses of PTMC without palpable thyroid nodes. Recently, studies have reported a good prognosis of PTMC. However, the rate of LNM has increased from 41% to 64%.²⁴ Although preoperative US is widely used, pathologically confirmed lymph nodes are not discovered before surgery. Kim et al.²¹ showed that the sensitivity and specificity of CLNM were 27.3%–55% and 69%–90%, and those of lateral LNM (LLNM) were 65%–90.3% and 82%–94.8%, respectively. The sensitivity and specificity of CLNM were 24.4% and 97.1%, and those of LLNM were 100.0% and 95.1%, respectively, in our study. The reduced sensitivity was largely due to failure

to detect positive nodes in the central neck. Because of the high incidence and low detection of CLNM, experts have proposed routine prophylactic dissection of cervical lymph nodes. Other experts oppose intervention because of the higher risks of surgery and postoperative complications of CLNM, especially in patients with PTMC without any features that are diagnostic of LNM either on a physical examination or preoperative US.²⁵ Our study investigated the preoperative predictive factors of central LNM that was missed by US in patients with PTMC, using clinicopathological and US features. This facilitated management of patients with PTMC. In our study, 149 of 218 patients with PTMC and LNM manifested central LNM, and 69 were detected, including 21 cases of LLNM. We analysed the clinicopathological and US features of patients who were missed. Larger tumour size (0.65 cm) and extrathyroidal invasion showed significant associations with central LNM, which is consistent with previous studies.^{25,26} Tumours with a diameter less than 0.65 were similar to those reported by Kim et al.²¹ Therefore, suspicion of PTMC with a larger tumour size (0.65 cm) or extracapsular invasion warrants further scrutiny. Early detection of these features is essential. Selective CCND may be helpful in patients who are diagnosed with PTMC.

There are several limitations in this study. First, our study only included patients with thyroid cancer from a similar environment. Second, although we reported the predictive factors of US images and discussed the clinical features of CLNM in patients with PTMC, we did not investigate the factors associated with long-term survival rates and loco-regional recurrence by continuous follow-up. Additional studies are required to address these issues.

In conclusion, our study shows that thyroid nodules with extrathyroidal invasion, the presence of microcalcification and multifocality, male sex, and age less than 47 years

are predictors of LNM. Primary tumours without extrathyroidal invasion and measuring less than 0.65 cm are risk factors for CLNM. Therefore, prediction of CLNM based on clinical and US factors is essential for appropriate surgical decisions and interventions.

Declaration of conflicting interest

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