ORIGINAL RESEARCH

Value of Combining Clinical Factors, Conventional Ultrasound, and Contrast-Enhanced Ultrasound Features in Preoperative Prediction of Central Lymph Node Metastases of Different Sized Papillary Thyroid Carcinomas

Yanfang Wang [iD][1]
Fang Nie[1]
Guojuan Wang[1]
Ting Liu[1]
Tiantian Dong[1]
Yamin Sun[2]

[1]Medical Center of Ultrasound, Lanzhou University Second Hospital, Lanzhou, Gansu, People's Republic of China; [2]Department of Pathology, Lanzhou University Second Hospital, Lanzhou, Gansu, People's Republic of China

Purpose: Early and accurate preoperative diagnosis of central lymph node metastasis (CLNM) is crucial to improve surgical management of patients with clinical lymph node-negative papillary thyroid carcinoma (PTC). Towards improving diagnosis of CLNM, we assessed the value of combining preoperative clinical characteristics, conventional ultrasound, and contrast-enhanced ultrasound (CEUS) in preoperative prediction of CLNM of different sized PTCs.

Patients and Methods: Patients were divided according to tumor size: a PTC group (>10 mm) and a papillary thyroid microcarcinoma (PTMC) group (≤10 mm). We retrospectively analyzed the clinical and ultrasonographic features of 120 PTC patients and 165 PTMC patients. Multivariate logistic regression analysis was used to screen independent risk factors and establish prediction models. Receiver operating characteristic curves were used to determine the best cut-off values for continuous variables and assess the performance of prediction models.

Results: Independent risk predictors of CLNM for the PTC group were extrathyroidal extension in CEUS (OR=7.923), tumor size >14 mm (OR=5.491), and multifocality (OR=3.235). For the PTMC group, the independent risk factors were the distance from the thyroid capsule =0 mm (OR=4.629), male (OR=3.315), tumor size >5 mm (OR=3.304), and microcalcification (OR=2.560). The predictive model of combined method had better performance in predicting CLNM of PTC compared with models based on CEUS and conventional ultrasound alone (area under the curve: 0.832 vs 0.739, *P*=0.0011; 0.832 vs 0.678, *P*=0.0012). For PTMC, comparing with CEUS, the combined method and conventional ultrasound performed better than CEUS alone in predicting CLNM (area under the curve: 0.783 vs 0.636, *P*=0.0016; 0.738 vs 0.636, *P*=0.0196).

Conclusion: The predictive models of combined method obtained from significant preoperative clinical and ultrasonographic features can potentially improve the preoperative diagnosis and individual treatment of CLNM in patients with PTC and PTMC. CEUS may be helpful in predicting CLNM of PTC, but CEUS would be ineffective in predicting CLNM of PTMC.

Keywords: papillary thyroid carcinoma, lymph node metastasis, prophylactic central neck dissection, ultrasonography, contrast-enhanced ultrasound

Correspondence: Fang Nie
Medical Center of Ultrasound, Lanzhou University Second Hospital, Chengguan District, Lanzhou, Gansu Province, 730030, People's Republic of China
Tel +86 0931 8942545
Email ery_nief@lzu.edu.cn

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Introduction

Papillary thyroid carcinoma (PTC) accounts for 84% of all thyroid carcinomas.[1] It is generally indolent, but 20% to 50% of patients with PTC acquire cervical lymph node metastasis, which is related to local tumor recurrence after initial surgery and disease-specific mortality.[2–5] Rigorous preoperative screening for cervical lymph node metastasis is crucial for planning PTC surgery.[6] There are two groups of cervical lymph node metastasis: central lymph node metastasis (CLNM) and lateral lymph node metastasis (LLNM). Usually, metastasis occurs first in central lymph nodes and then in lateral lymph nodes according to the lymphatic drainage pathway.[7] CLNM has a relatively high prevalence in PTC patients, ranging from 25% to 57.9%; the prevalence of lateral lymph node metastasis was reported to be 15%–25.6%.[8–10]

Currently, clinicians often use high-resolution conventional ultrasound as the initial noninvasive imaging method to preoperatively assess cervical lymph node status of PTC.[3] Ultrasound-guided fine-needle aspiration is the recommended method for preoperative diagnosis of sonographically suspicious lymph nodes ≥8–10 mm in the smallest diameter.[3] However, only 20% to 31% of suspicious cervical lymphadenopathy can be identified by ultrasonography preoperatively because of the presence of the overlying thyroid gland.[11–13] A meta-analysis conducted by Zhao et al[14] revealed that preoperative ultrasound had poor sensitivity (0.33) in the diagnosis of CLNM of PTC and relatively good sensitivity (0.70) in diagnosis of LLNM of PTC. Considering the higher prevalence of CLNM and poor performance of preoperative conventional ultrasound in detecting CLNM, clinicians usually perform prophylactic central lymph node dissection. However, prophylactic central lymph node dissection is not necessary for individuals with low-risk PTC. In addition, the medical community has recently tended to be more conservative for the management of low-risk PTC.[15,16] If appropriately used, active surveillance for low-risk tumors, especially for papillary thyroid microcarcinoma (PTMC), is a safe management strategy that offers favorable outcomes and preserves quality of life at low cost.[16]

To improve the diagnosis of CLNM of PTC, researchers have increasingly attempted to predict CLNM with clinicopathologic characteristics and ultrasonographic features of primary PTC or PTMC.[9,17,18] However, the indicators used in past studies were mainly postoperative histopathologic characteristics or preoperative conventional ultrasound features. In addition, the risk factors varied for different sized papillary thyroid carcinomas. Contrast-enhancedultrasound (CEUS), highly regarded in ultrasound medicine, has been used to visualize the microvascularization that is important for tumor distribution and neoplastic growth.[19,20] Several studies have shown that CEUS could assess the biological behavior of thyroid nodules.[21–23] To our knowledge, few studies have included CEUS for preoperative prediction CLNM of different sized PTC.

In this retrospective study, to improve the preoperative diagnosis of CLNM and assist the clinical selection of individual central lymph node dissection for patients with PTC, we divided PTC patients into two groups (>10 mm and ≤10 mm). We analyzed the preoperative clinical characteristics, conventional ultrasound features, and CEUS features in different sized tumor groups to assess the value of these features in preoperative prediction of CLNM of papillary thyroid carcinomas.

Materials and Methods
Patients

This retrospective study was conducted in accordance with the Declaration of Helsinki. The Ethics Committee of Lanzhou University Second Hospital approved the study. All patients signed informed consent before CEUS examination and surgery.

We reviewed the clinical, pathological, and ultrasonographic materials of consecutive surgically confirmed PTC or PTMC patients at Lanzhou University Second Hospital from January 2018 to November 2020. Patients were enrolled according to the following criteria: (a) both conventional ultrasound and CEUS examination for each nodule within one month before surgery; (b) no evidence of cervical node metastasis or distance metastasis on preoperative ultrasound or computed tomography; (c) prophylactic central compartment lymph node dissection (for unilateral tumor: thyroidectomy, isthmectomy, and ipsilateral central compartment lymph node dissection; for bilateral tumor: total thyroidectomy and bilateral central compartment lymph node dissection); (d) no previous thyroid operation history. The exclusion criteria were the following: (a) inconsistent tumor on ultrasound and pathology based on location and size; (b) maximum diameter of the primary tumor <5 mm (too small to be observed on CEUS because of respiratory motion and the volume effect). Ultimately, two hundred eighty-five

patients with 285 nodules (72 men, 213 women, mean age, 44.2 ± 11.7 years; age range, 21–76 years) were included in the study. Tumor size ranged from 5 mm to 40 mm (mean size of 11.9 ± 6.8mm). Sex, age, Hashimoto's thyroiditis, multifocality, bilaterality, extrathyroidal extension, and central lymph node status were collected from medical records.

Conventional Ultrasound

Conventional ultrasound images of thyroid nodules were obtained by the Philips iU22 scanner with a 5–12 MHz linear probe and the ACUSON Sequoia scanner with a 4–10 linear probe. The patient was placed on a bed in the supine position and the neck region was fully exposed. Conventional ultrasound images of thyroid nodules were acquired by carefully scanning the thyroid and adjacent tissues both transversely and longitudinally and stored in the internal hard disk of the instrument for further analysis. We defined the target thyroid nodules as nodules with suspicious malignant ultrasound features (solid component, (marked) hypoechogenicity, microlobulated or irregular margins, microcalcifications, and taller-than-wide shape).[24] If multiple nodules with suspicious malignant ultrasound features were present, the nodule with the largest diameter or the most numbers of suspicious malignant features was the target thyroid nodule, and we defined this condition as multifocality.

The ultrasonic examinations were performed by two radiologists with more than five years of experience in thyroid examination. The conventional ultrasound features of the target nodules were evaluated as the following: tumor location (left or right lobe; upper 1/3, middle 1/3, or lower 1/3 part of the lobe), tumor size (the maximum diameter among three diameters); distance from the thyroid capsule, which means the distance of the edge of the thyroid tumor from the thyroid capsule (Figure 1A), was classified as >0 mm (Figure 1A) and =0 mm (the edge of a tumor abutted the thyroid capsule or trachea (Figure 2A); echogenicity (hyperechoic/isoechoic, hypoechoic or marked hypoechoic); shape (wider than tall or taller and wide); margin (regular – well circumscribed or irregular – irregular/microlobulated); and microcalcification (absent or present).

Contrast-Enhanced Ultrasound

Contrast-enhanced ultrasound (CEUS) examination was conducted using the same instrument as for conventional ultrasound with a 3–9 MHz or 4–10 MHz linear probe.

CEUS was performed using a low mechanical index (< 0.10) to minimize destruction of microbubbles and loss of artificial signals. The plane with the maximum nodular size and an appropriate amount of surrounding parenchyma was selected in each nodule for CEUS. Patients were instructed to stop swallowing and to breathe calmly throughout the process. The contrast agent (SonoVue, Bracco, Italy) was mixed with 5 mL of saline until a homogeneous mixed suspension was obtained. Then, 1.8–2.0 mL of the suspension was rapidly pushed into the patient's peripheral vein via a probe while their body position remained unchanged. The ultrasound machine timer was activated while the contrast agent was injected. Each contrast imaging acquisition lasted for at least two continuous minutes, and the process was recorded on the instrument's internal hard drive.

For CEUS, according to previous articles[21,25] and our clinical experience, thyroid nodules were evaluated with the following characteristics: homogeneity of enhancement, classified as homogeneous or heterogeneous; enhanced intensity (with respect to the surrounding normal thyroid parenchyma) was classified as hyper-enhancement, iso-enhancement or hypo-enhancement; ring enhancement (hyperechoic rim in the periphery of a nodule at the peak intensity), was classified as present (regular and complete) or absent (no, irregular or incomplete); enhanced border (the boundary between the nodule and the surrounding parenchyma at the peak intensity), was classified as well-defined or ill-defined; extrathyroidal extension (the thyroid nodule's enhancement range contacted/discontinued the hyperechoic thyroid capsule or extended out of the thyroid capsule)[26] was classified as no or yes (Figures 1C and 2C); centripetal enhancement (the contrast agent enters the nodule from the periphery of the nodule to the center), was classified as yes or no; the relative time of wash-in (using the surrounding normal thyroid parenchyma as a reference), was classified as earlier, concurrent, or later; and the relative time of wash-out time (using the surrounding normal thyroid parenchyma as a reference), was classified as earlier, concurrent, or later.

Imaging Analysis

Two experienced radiologists (TL and TT D) with >5 years of experience reviewed conventional ultrasound and CEUS images and cine clips. The radiologists were blinded to patient clinical information and pathology results. In case of discrepancy between the two radiologists, a consensus was reached by discussion.
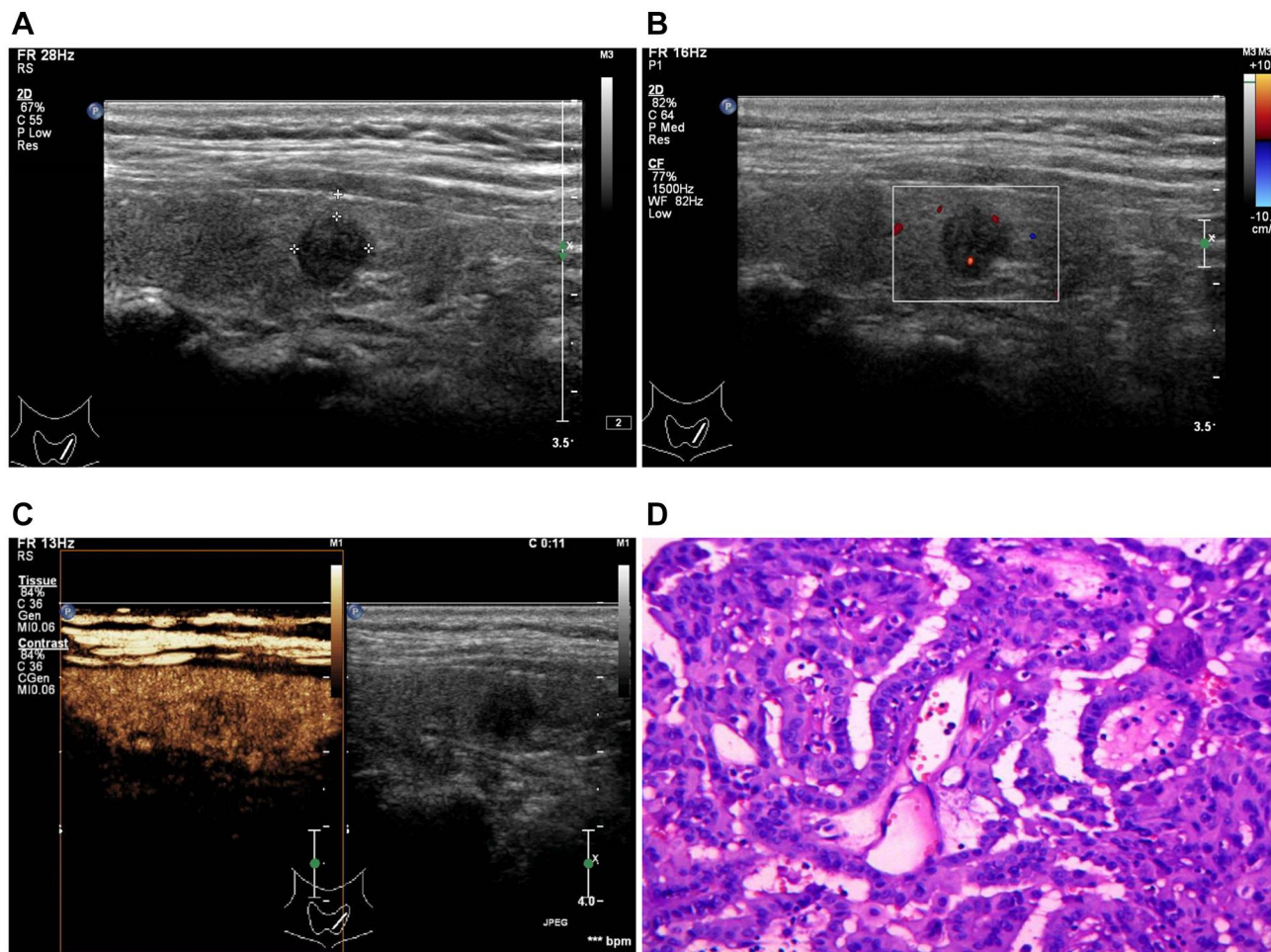
Figure 1 An 8mm papillary thyroid carcinoma without central cervical lymph node metastasis in a 55-year-old woman. (**A**) Gray-scale ultrasound shows a marked hypoechoic nodule in the left lobe of the thyroid, with a measurement of nodule size and a distance from the adjacent thyroid capsule. (**B**) Sparse intranodular and peripheral blood flow signal is found on color Doppler imaging. (**C**) On contrast-enhanced ultrasound, comparing with the normal thyroid parenchyma, the nodule shows inhomogeneous hypo-enhancement, with clear enhanced border, no ring enhancement, and no extrathyroidal extension. (**D**) Papillary thyroid carcinoma was confirmed by pathology (hematoxylin-eosin stain, ×400 magnification).

Pathological Diagnosis

All surgical tumor specimens were categorized by experienced pathologists who were blinded to patient medical history and ultrasonographic findings. Tumor location, tumor size, extrathyroidal extension, and central and/or lateral lymph node status were recorded in the pathology reports and reassessed by an experienced pathologist (YM S). When there was disagreement with previous reports, consensuses were reached by discussion with the previous pathologists.

Statistical Analysis

SPSS software (version 22.0, IBM Corporation, Armonk, NY, USA) was used for statistical analysis. A two-tailed p-value of <0.05 was considered statistically significant.

Data of continuous variables are shown as mean ± standard deviation, number and percent of categorical variables. The independent t-test or Mann–Whitney U-test was used for comparing continuous variables and chi-squared test or Fisher's exact test was conducted for categorical variables. Variables that were clinically relevant or that showed a univariate significance with CLNM were entered into a multivariate logistic regression analysis with a forward stepwise method to ascertain the independent risk factors and establish prediction models. The receiver operating characteristic (ROC) curves obtained by MedCalc were used to determine the best cut-off values for the continuous variables (tumor size and distance from the thyroid capsule) and assess models' diagnostic performance. The corresponding area under the curve (AUC), sensitivity, and specificity were calculated at the optimal cut-off values.
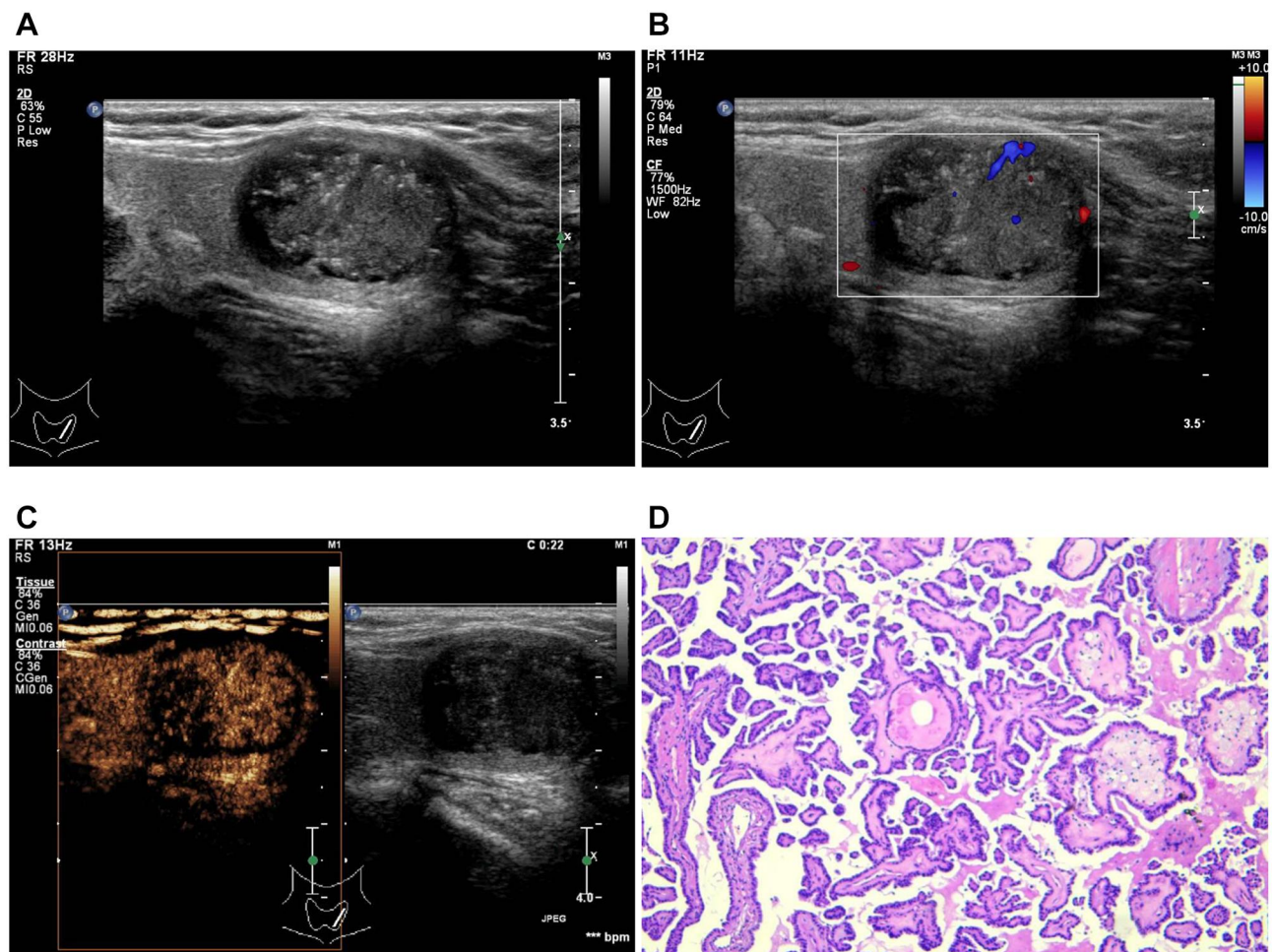
Figure 2 A 24mm papillary thyroid carcinoma with central cervical lymph node metastasis in a 37-year-old woman. (**A**) Gray-scale ultrasound shows a heterogeneous nodule in the left lobe of the thyroid, with a regular margin and microcalcification within the nodule. The adjacent thyroid capsule is continuous but protruded outward by the nodule. (**B**) Intranodular and peripheral blood flow signal is found on color Doppler imaging. (**C**) On contrast-enhanced ultrasound, comparing with the normal thyroid parenchyma, the tumor shows inhomogeneous hypo-enhancement, with partially clear enhanced border and incomplete ring enhancement. The adjacent thyroid capsule is discontinuous, which indicates an extrathyroidal extension. (**D**) Papillary thyroid carcinoma was confirmed by pathology (hematoxylin-eosin stain, ×200 magnification).

Results

Basic Characteristics

We enrolled 285 patients with 285 papillary thyroid (micro)carcinomas. According to WHO classification[27] and the pathology reports, we further divided the patients into a PTC group (tumor size >10mm, n=149) and a PTMC group (tumor size ≤10mm, n=165). Table 1 summarizes the demographic and clinical characteristics of PTC patients. Of the 120 PTC patients, 57 (55.8%) had CLNM. Among the 165 PTMC patients, 45 (27.3%) had CLNM. Tumor size ($P<0.001$) and tumor location ($P=0.048$) were significantly different between with and without CLNM in the PTC group. Sex ($P=0.002$) and tumor size ($P=0.004$) showed differences between with and without CLNM in the PTMC group.

We converted continuous variables (tumor size and the distance from the capsule) into classification variables according to ROC curves (Supplementary Figures 1 and Supplementary Figure 2). The best cut-off value of tumor size and distance from the capsule in PTC for discriminating with and without CLNM was >14.0 mm and >0 mm, with an AUC of 0.714 and 0.605, respectively. The best cut-off value of tumor size and distance from the capsule in PTMC was >5.0 mm and >0 mm, with an AUC of 0.645 and 0.719, respectively.

Agreement Between Extrathyroidal Extension in Preoperative CEUS and Postoperative Pathology

We compared the data of preoperative CEUS and postoperative pathology for the diagnosis of extrathyroidal

Table 1 Basic Characteristics

Indicators		PTC (>10mm) with CLNM			PTMC (≤10mm) with CLNM		
		No (n=53)	Yes (n=67)	P	No (n=120)	Yes (n=45)	P
Sex	Female	39 (73.6)	44 (65.7)	0.351*	101 (84.2)	28 (62.2)	0.002*
	Male	14 (26.4)	23 (34.3)		19 (15.8)	17 (37.8)	
Age (y)		46.1 ± 11.1	43.3± 13.5	0.235#	44.4 ± 11.0	42.5± 11.4	0.550#
	< 55	43 (81.1)	54 (80.6)	0.941*	101 (84.2)	35(77.8)	0.337*
	≥ 55	10 (18.9)	13 (19.4)		19 (15.8)	10(22.2)	
Size(mm)	Mean	14.0	18.0	<0.001^	7.0	8.0	0.004^
Multifocality	No	37 (69.8)	38 (56.7)	0.141*	65 (54.2)	22 (38.9)	0.545*
	Yes	16 (30.2)	29 (43.3)		55 (45.8)	23 (51.1)	
Bilaterality	No	41 (77.4)	44 (65.7)	0.162*	68 (56.7)	26 (57.8)	0.589*
	Yes	12 (22.6)	23 (34.3)		52 (43.3)	19 (42.2)	
Location	Upper	18 (34.0)	10 (14.9)	0.048*	32 (26.7)	12 (26.7)	0.451*
	Middle	18 (34.0)	31 (46.3)		46 (38.3)	13 (28.9)	
	Lower	17 (32.1)	26 (38.8)		42 (35.0)	20 (44.4)	
Hashimoto's thyroiditis	Absent	40 (75.5)	52 (77.6)	0.783*	72 (60.0)	32 (71.1)	0.188*
	Present	13 (25.5)	15 (22.4)		48 (40.0)	13 (28.9)	

Notes: *Determined with the χ^2 test; #determined with the independent sample t-test; ^determined with the Mann–Whitney U-test.
Abbreviations: PTC, papillary thyroid carcinoma; PTMC, papillary thyroid microcarcinoma; CLNM, cervical lymph node metastasis.

extension. There was moderate agreement between the two methods (κ = 0.636, $P < 0.001$; Table 2).

Univariate and Multivariate Analysis on the Predictors of CLNM of the PTC Group

Table 3 shows that size >14.0 mm, echogenicity, distance from thyroid capsule = 0 mm, homogeneous enhancement, and presence of extrathyroidal extension were more frequently found in the PTC group of patients with CLNM (all $P < 0.05$). Shape, margin, microcalcification, peak intensity, ring enhancement, enhanced border, centripetal enhancement, time of wash-in, and time of wash-out did not differ significantly with and without CLNM (all $P > 0.05$).

Table 2 Agreement of Extrathyroidal Extension in Preoperative CEUS and Postoperative Pathology

Preoperative CEUS	Postoperative Pathology		κ	P&
	No	Yes		
No	124 (96.9)	49 (31.2)	0.636	<0.001
Yes	4 (3.1)	108 (68.8)		

Note: &Determined with the Cohen's kappa test.
Abbreviation: CEUS, contrast-enhancement ultrasound.

Multivariate logistic regression was performed for all significant variables and clinically relevant variables. Table 5 summarizes all independent variables. Odds ratio (OR) >1 indicates risk factors. Presence of extrathyroidal extension (OR=7.923, $P<0.001$), tumor size > 14.0 mm (OR=5.491, P=0.001), and multifocality (OR=3.235, P=0.024) were independent risk predictors for CLNM of PTC. We established a predictive model based on the foregoing multivariate logistic regression: Logit (P) = −2.394 + 2.070×Extrathyroidal extension + 1.703×Size + 1.174×Multifocality, where the categorical variables were assigned as "1" if presence of independent risk predictors and "0" if absence.

Univariate and Multivariate Analysis on the Predictors of CLNM of the PTMC Group

As shown in Table 4, CLNM in patients with PTMC was significantly associated with sex, size, microcalcification, the distance from the thyroid capsule, and extrathyroidal extension.

Multivariate logistic regression analysis showed the independent predictive factors were the distance from the thyroid capsule = 0 mm (OR=4.629, $P<0.001$), male (OR=3.315, P=0.008), size (OR=3.304, P=0.043), and presence of microcalcification (OR=2.207, P=0.048) (Table 5). The established predictive model was the

Table 3 Univariate Analysis of CLNM in PTC Group

Parameters		Central Lymph Node Metastasis		P*
		No (n=53)	**Yes (n=67)**	
Size (mm)	≤14.0	34 (64.2)	18 (26.9)	<0.001
	>14.0	19 (35.8)	49 (73.1)	
Conventional ultrasound features				
Echogenicity	Hyper/Isoechoic	4 (7.5)	5 (7.5)	0.020
	Hypoechoic	35 (66.1)	57 (85.0)	
	Marked hypoechoic	14 (26.4)	5 (7.5)	
Shape	Wider than tall	33 (62.3)	42 (62.7)	0.962
	Taller than wide	20 (37.7)	25 (37.3)	
Margin	Regular	15 (28.3)	14 (20.9)	0.347
	Irregular	38 (71.7)	53 (79.1)	
Micro-calcification	No	22 (41.5)	21 (31.3)	0.249
	Yes	31 (58.5)	46 (68.7)	
Distance from thyroid capsule	> 0 mm	18 (34.0)	7 (10.4)	0.002
	= 0 mm	35 (66.0)	60 (89.6)	
Contrast-enhanced ultrasound features				
Homogeneity	Homogeneous	4 (7.5)	2 (3.0)	0.046
	Heterogeneous	49 (92.5)	65 (97.0)	
Peak Intensity	Hyper-enhancement	11 (20.8)	21 (31.3)	0.323
	Iso-enhancement	10 (18.9)	8 (11.9)	
	Hypo-enhancement	32 (60.4)	38 (56.7)	
Ring enhancement	Present	5 (9.4)	5 (7.5)	0.748
	Absent	48 (90.6)	62 (92.5)	
Enhanced border	Well-defined	20 (37.7)	21 (31.3)	0.463
	Ill-defined	33 (62.3)	46 (68.7)	
Extrathyroidal extension	No	34 (64.2)	11 (16.4)	<0.001
	Yes	19 (35.8)	56 (83.6)	
Centripetal	No	26 (49.1)	29 (43.3)	0.529
	Yes	27 (50.9)	38 (56.7)	
Time of wash-in	Concurrent	7 (13.2)	9 (13.4)	0.621
	Later	32 (60.4)	35 (52.2)	
	Earlier	14 (26.4)	23 (34.3)	
Time of wash-out	Concurrent	5 (9.4)	7 (10.4)	
	Later	13 (24.5)	12 (17.9)	0.675
	Earlier	35 (66.0)	48 (71.6)	

Note: *Determined with the χ^2 test.
Abbreviations: CLNM, central lymph node metastasis; PTC, papillary thyroid carcinoma.

following: Logit (*P*) = −3.505 + 1.532×Distance from the thyroid capsule + 1.199×Sex + 0.940×Micro-calcification + 1.195×Size, where the categorical variables were assigned as "1" if presence of independent risk predictors and "0" if absence.

ROC Curve Analysis

We performed ROC curve analysis of three methods (conventional ultrasound, CEUS, and combined method) in predicting CLNM for the PTC group and PTMC group (Figure 3). The AUC of the combined method in predicting

Table 4 Univariate Analysis of CLNM in PTMC Group

Parameters		Central Lymph Node Metastasis		P*
		No (n=120)	Yes (n=45)	
Size (mm)	= 5.0	36 (30.0)	4 (8.9)	0.005
	>5.0	84 (70.0)	41 (91.1)	
Conventional ultrasound features				
Echogenicity	Hyper/Isoechoic	5 (4.2)	1 (2.2)	0.780
	Hypoechoic	91 (75.8)	36 (80.0)	
	Marked hypoechoic	24 (20.0)	8 (17.8)	
Shape	Wider than tall	47 (39.2)	24 (53.3)	0.102
	Taller than wide	73 (60.8)	21 (46.7)	
Margin	Regular	23 (19.2)	8 (17.8)	0.839
	Irregular	97 (80.8)	37 (82.2)	
Micro-calcification	No	84 (70.0)	20 (44.4)	0.002
	Yes	36 (30.0)	25 (55.6)	
Distance from thyroid capsule	> 0 mm	77 (64.2)	12 (26.7)	<0.001
	= 0 mm	43 (35.8)	33 (73.3)	
Contrast-enhanced ultrasound features				
Homogeneity	Homogeneous	19 (15.8)	5 (11.1)	0.444
	Heterogeneous	101 (84.2)	40 (88.9)	
Peak Intensity	Hyper-enhancement	17 (14.2)	4 (8.9)	0.504
	Iso-enhancement	15 (12.5)	8 (17.8)	
	Hypo-enhancement	88 (73.3)	33 (73.3)	
Ring enhancement	Present	3 (2.5)	2 (4.4)	0.614
	Absent	117 (97.5)	43 (95.6)	
Enhanced border	Well-defined	37 (30.8)	9 (20.0)	0.167
	Ill-defined	83 (69.2)	36 (80.0)	
Extrathyroidal extension	No	102 (85.0)	26 (57.8)	<0.001
	Yes	18 (15.0)	19 (42.2)	
Centripetal	No	49 (40.8)	15 (33.3)	0.379
	Yes	71 (59.2)	30 (66.7)	
Time of wash-in	Concurrent	13 (10.8)	5 (11.1)	0.358
	Later	91 (75.8)	30 (66.7)	
	Earlier	16 (13.3)	10 (22.2)	
Time of wash-out	Concurrent	16 (13.3)	6 (13.3)	
	Later	14 (11.7)	7 (15.6)	0.796
	Earlier	90 (75.0)	32 (71.1)	

Note: *Determined with the χ^2 test.
Abbreviations: CLNM, central lymph node metastasis; PTMC, papillary thyroid microcarcinoma.

CLNM of PTC was 0.832, significantly higher than the 0.739 AUC for CEUS (P=0.0011) and the AUC=0.678 for conventional ultrasound (P=0.0012) alone (Figure 3A). In predicting CLNM of PTC, the sensitivity and specificity of CEUS (83.6% and 64.2%) were higher than that of conventional ultrasound (74.6% and 56.6%), but there was no statistical difference (P=0.2236) (Figure 3A, Table 6). The combined method had a sensitivity of 80.6% and a specificity of 79.3% in predicting CLNM of PTC (Table 6). For the PTMC, conventional ultrasound (AUC=0.738,

Table 5 Multivariate Logistic Regression of CLNM in PTC Group and PTMC Group

Indicators		B	P#	OR (95% CI)
PTC group				
Extrathyroidal extension	Yes vs No	2.070	<0.001	7.923 (3.155–19.898)
Size (mm)	> 14.0 vs ≤ 14.0	1.703	0.001	5.491 (2.101–14.347)
Multifocality	Yes vs No	1.174	0.024	3.235 (1.171–8.937)
Constant	–	−2.394	<0.001	0.091
PTMC group				
Distance from thyroid capsule (mm)	=0 vs > 0	1.532	<0.001	4.629 (2.061–10.396)
Sex	Male vs female	1.199	0.008	3.315 (1.365–8.051)
Micro-calcification	Yes vs No	0.940	0.020	2.560 (1.158–5.657)
Size (mm)	> 5.0 vs = 5.0	1.195	0.043	3.304 (1.036–10.537)
Constant	-	−3.505	<0.001	0.030

Notes: B, regression coefficient; #determined with the logistic regression analysis.
Abbreviations: CLNM, central lymph node metastasis; PTC, papillary thyroid carcinoma; PTMC, papillary thyroid microcarcinoma; OR, odds ratio.

sensitivity=73.3%, specificity=64.2%) had better performance than CEUS (AUC=0.636, sensitivity=42.2%, specificity=85.0%) in predicting CLNM (P=0.0196) (Figure 3B, Table 6). The combined method's AUC was 0.783, which was higher than CEUS (P=0.0016) alone but not higher that the AUC of conventional ultrasound (P=0.0580) alone (Figure 3B). The sensitivity and specificity of the combined method in predicting CLNM of PTMC were 60.0% and 86.7%, respectively (Table 6).

Discussion

In this study, we divided the PTC patients into a PTC group (>10 mm) and a PTMC group (≤10 mm) and analyzed the clinical characteristics, conventional ultrasound features, and CEUS features of primary tumors to investigate their preoperative predictive performance for CLNM. By univariate and multivariate analysis, we found that the presence of extrathyroidal extension, size >14.0 mm, and multifocality were independent predictors for the PTC
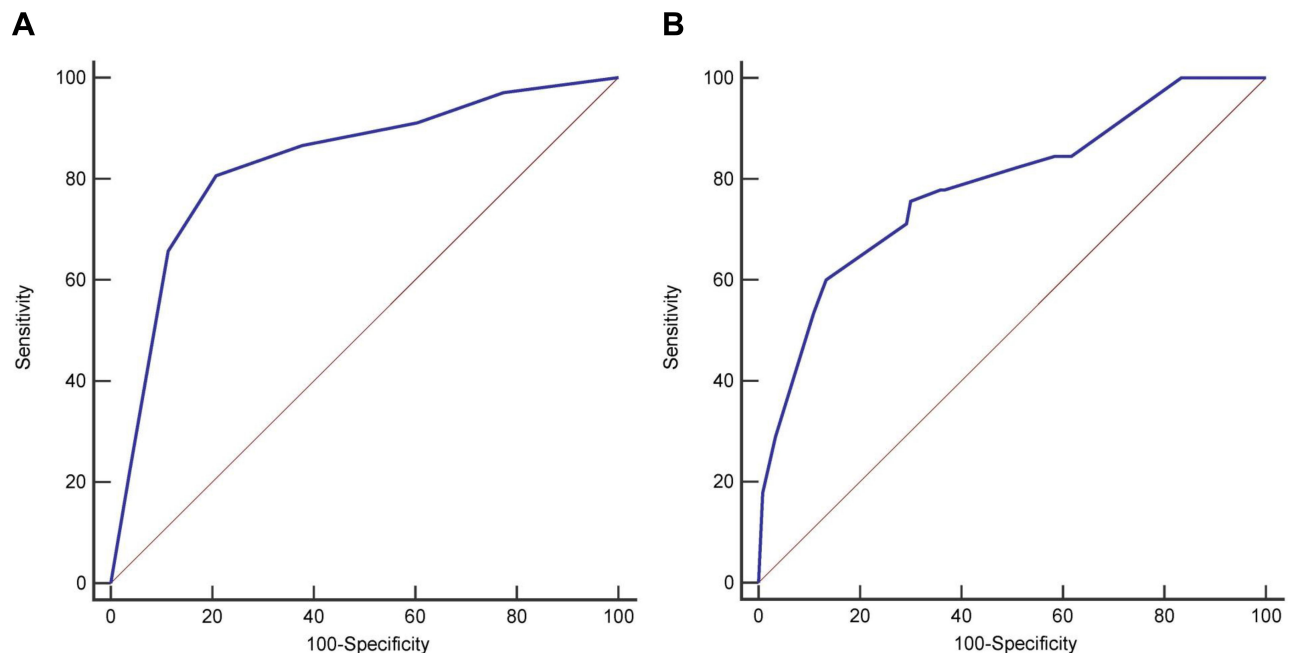
Figure 3 ROC curves analysis. (**A**)AUC of combined method in the papillary thyroid carcinoma group: (0.832). (**B**) AUC of combined method in the papillary thyroid microcarcinoma group: (0.783).
Abbreviations: ROC, receiver operating characteristic curves; AUC, area under the curve; CEUS, contrast-enhanced ultrasound.

Table 6 ROC Analysis of Prediction Model in Diagnosing CLNM of PTC and PTMC

	AUC	Youden Index	Sensitivity	Specificity
PTC group				
Prediction model	0.832 (0.753–0.894)	0.598	80.6%	79.3%
CEUS	0.739 (0.651–0.815)	0.477	83.6%	64.2%
Conventional US	0.678 (0.587–0.761)	0.312	74.6%	56.6%
PTMC group				
Prediction model	0.783 (0.712–0.843)	0.467	60.0%	86.7%
CEUS	0.636 (0.558–0.709)	0.272	42.2%	85.0%
Conventional US	0.738 (0.664–0.803)	0.375	73.3%	64.2%

Abbreviations: ROC, receiver operating characteristic curves; CLNM, cervical lymph node metastasis; PTC, papillary thyroid carcinoma; PTMC, papillary thyroid microcarcinoma; AUC, area under the curve; CEUS, contrast-enhanced ultrasound; US, ultrasound.

group of patients with CLNM. For the PTMC group of patients with CLNM, the predictors were a distance from the thyroid capsule =0 mm, male, size >5.0 mm, and the presence of microcalcification. CEUS may be helpful in predicting CLNM of PTC, but it would be of limited value in predicting CLNM of PTMC.

Angiogenesis has an important function in the development, growth, and metastasis of a tumor. PTC can spread to regional lymph nodes through newly formed or preexisting vessels.[28] Currently, clinicians use CEUS as a supplement to conventional ultrasound to visualize the microvasculature and offer details of a tumor. Wei et al[21] found that CEUS had a higher sensitivity and specificity in the diagnosis of extrathyroidal extension compared with conventional ultrasound (91.1% and 86.5% vs 49.0% and 55.0%). In our study, we used CEUS to assess the extrathyroidal extension. In univariate analysis of eight CEUS features, we found that extrathyroidal extension was associated with CLNM for both the PTC group and PTMC group. Fortunately, the use of CEUS to detect extracapsular extension presented moderate agreement between the preoperative CEUS and postoperative pathology (κ=0.636, P <0.001). Multivariate analysis showed that extrathyroidal extension was an independent risk factor for the PTC group (OR=7.923, P<0.001) but not for the PTMC group. This finding was partly in line with previous studies.[23,29] As shown in Tables 3 and 5, extrathyroidal extension in the PTC group with CLNM (83.6%, 56/67) was nearly two times greater than that of the PTMC group with CLNM (42.2%, 19/45). For further analysis, among the 95 PTC patients with the distance from the capsule = 0 mm, we observed CLNM in 90% (54/60) with extrathyroidal extension and 10% (6/60) without extrathyroidal extension. In the 76 PTMC patients with the distance from the capsule = 0 mm, we found CLNM in 57.6% (19/33) with extrathyroidal extension and 42.4% (14/33) without

extrathyroidal extension. These findings suggested that, although all were tumors with the distance from the capsule = 0 mm, CLNM more frequently occurred in the PTC group with extrathyroidal extension. Therefore, extracapsular extension was an important independent risk factor of CLNM in larger PTC.

Although PTC can occur anywhere within the thyroid gland, we found CLNM was more likely to occur in the location close to the thyroid capsule. We used the distance of the edge of the tumor from the thyroid capsule in conventional ultrasound to assess its relationship with the CLNM of PTC. Both univariate analysis and multivariate regression analysis revealed that the distance from the capsule = 0 mm (namely, subcapsular) was closely associated with the PTMC group with CLNM (OR=4.629, P <0.001). This result seemed to be consistent with a recent study by Tallini et al[30] that indicated that larger subcapsular PTMC represents the most aggressive behavior, such as lymph node metastasis. It is not surprising that subcapsular PTMC have easy access to the capsule and extrathyroidal tissues, including vascular and lymphatic vessels.

Tumor size has been used for tumor management and staging.[31] Large tumor diameter is associated with lymph node metastasis and recurrence.[32,33] Previous studies[18,33,34] have shown that a tumor size >10 mm was an independent risk factor for CLNM of PTC. We divided tumors into two groups: ≤10 mm (PTMC group) and >10 mm (PTC group). Both univariate analysis and multivariate analysis revealed that the larger tumor size in preoperative ultrasound was associated with CLNM. For the PTMC group, a tumor >5.0 mm was an independent predictor for CLNM of PTMC. Zhang et al[35] reported the same result. For the PTC group, a tumor >14.0 mm was associated with CLNM. The cut-off value in our investigation was lower compared with

previous studies that reported a value of 20 mm.[36,37] This difference may be related to sample size and selection bias. Therefore, an accurate measurement of tumor size in preoperative ultrasound is helpful in the management of suspicious thyroid nodules.

Multifocality often occurs at an early stage in patients with PTC, and Yao et al[38] used multifocality as an independent risk factor for CLNM. However, some patients had microscopic PTC (an incidental finding for patients treated surgically for presumably benign thyroid diseases).[39] Microscopic PTC are a detection challenge for radiologists prior to surgery. To avoid a possible detection limitation, we set the criteria of multifocality as two or more thyroid lesions all with suspicious malignant ultrasound features. The OR value of multifocality (OR=3.235) in the PTC group with CLNM in our study was higher than that (OR=1.297) reported by Liu et al,[40] who included both benign and malignant nodules in multifocality Therefore, it would be better to use multiple lesions all with suspicious malignant features as multifocality in predicting CLNM of PTC patients.

In women, the incidence of PTMC is much higher but the rate of CLNM is lower than in men.[41] Our findings supported previous observations that being male was an independent risk factor for CLNM of PTMC patients.[18,33,35] Nonetheless, the association between sex and CLNM of PTMC remains controversial. Wu et al and Jeon et al did not find an association between sex and CLNM of PTMC.[36,42] This absence of association may have been due to selection bias. Combining multiple risk factors is necessary in clinical practice.

Microcalcification is common in PTC and rare in other pathological types of thyroid cancer. In our study, the prevalence of microcalcification in the PTC group was 64.2% (77/120) and 37.0% (61/165) in the PTMC group; these frequencies were greater than those reported by Ha et al (30.5%, 108/354) and Oh et al (35.9%, 136/379).[43,44] The difference could be attributed to our classification of microcalcification; we included other types of calcification with microcalcification. Besides, microcalcification in the PTMC group with CLNM was greater than without CLNM (55.6% vs 30.0%, P=0.002). We did not find a significant difference in the PTC group (68.7% vs 58.5%, P=0.249). This result suggested that microcalcification (or a mix with other types of calcification) occurs more frequently in larger PTC regardless of CLNM. The reason for this phenomenon is not clear, but it may be related to calcium phosphate deposits.[45] Like the present results, previous studies have demonstrated that calcification is associated with CLNM compared with the absence of calcification in PTMC patients.[44]

Because of the low sensitivity of conventional ultrasound in detecting CLNM, we adopted a combination of clinical characteristics, conventional ultrasound features, and CEUS features to improve diagnostic sensitivity. By multivariate logistic regression analysis in predicting CLNM of PTC and PTMC, we established two prediction models based on significant clinical and ultrasonographic features (combined method). For the PTC group, the prediction model of combined method had significantly better performance in predicting CLNM than the predictive ability of CEUS (P=0.0011) and conventional ultrasound (P=0.0012) alone, with a sensitivity of 80.6% and a specificity of 79.3%. CEUS had a higher sensitivity (83.6% vs 82.1%) and specificity (64.2% vs 49.1%) compared with conventional ultrasound, but there was no statistical difference between the two sonographic methods alone (P=0.2236). However, the predictors for CLNM of PTC (extrathyroidal extension, size, and multifocality) did not include conventional ultrasound features; the lack of conventional ultrasound features inclusion indicated that the clinical factors and extrathyroidal extension in CEUS were more helpful in predicting CLNM of PTC. For the PTMC group, the prediction model and conventional ultrasound has significantly better performance than CEUS alone (0.783 vs 0.636, P=0.0016; 0.738 vs 0.636, P=0.0196). There was no difference between the prediction model and conventional ultrasound (P=0.0580), which suggested that conventional ultrasound was more helpful than CEUS in predicting CLNM of PTMC. This phenomenon was also mirrored by the predictors of CLNM. Therefore, we conclude that CEUS may be more helpful in predicting CLNM of PTC, but CEUS is limited in predicting CLNM for PTMC. For predicting CLNM of PTMC, we should mainly focus on conventional ultrasound features (micro-calcification and distance from the capsule) and clinical factors (tumor size and patient sex).

There were some limitations to this study. First, this study was retrospective, which had the inevitable feature of being nonrandomized. Second, this study was single-center with a small sample size; a multicenter prospective study with larger sample size is needed to validate the diagnostic accuracy of our predictive models. Third, the analysis of ultrasound images was qualitative and inevitably influenced by human factors. Radiomics, which turn medical images into mineable data by extracting high-throughput features quantitatively, may be available in the near future to estimate cervical lymph metastasis of PTC.

Conclusion

The prediction models based on preoperative clinical and ultrasonographic features in this study have the potential to improve the preoperative diagnosis of CLNM of patients with PTC and PTMC. Patients without the independent risk factors may benefit if they do not undergo prophylactic central lymph node dissection. CEUS may be helpful in predicting CLNM of PTC, but CEUS is not likely to be helpful in predicting CLNM of PTMC.

Ethics Approval and Informed Consent

This study was approved by the Ethics Committee of Lanzhou University Second Hospital. Written informed consent was obtained from all patients.

Acknowledgments

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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