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Factors of Central Lymph Node Metastasis in Papillary Thyroid Cancer Based on C-TIRADS Analysis

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ABSTRACT

To study risk factors for central lymph node metastasis (CLNM) in papillary thyroid cancer (PTC) using the Chinese Thyroid Imaging Reporting and Data System (C-TIRADS). We retrospectively analysed patients who underwent PTC surgery and central lymph node dissection at First People's Hospital of Foshan City. The clinical and ultrasonic data of the patients from 1150 cases were analysed by multivariate regression to evaluate the correlation between grayscale ultrasound (US) features, C-TIRADS score, and the classification of thyroid nodules and CLNM of PTCs. The C-TIRADS score was 3.0 ± 1.0 in the CLNM group, which was higher than that in the non-CLNM group ($p < 0.001$). Sex (male) (OR = 1.586, 95 % CI 1.232–2.042, $p < 0.001$), age (≤ 45 years) (OR = 1.508, 95 % CI 1.184–1.919, $p = 0.001$), location of nodes (lower pole) (OR = 2.193, 95 % CI 1.519–3.166, $p < 0.001$), number (multifocal) (OR = 2.204, 95 % CI 1.227–2.378, $p < 0.001$), microcalcification (OR = 1.610, 95 % CI 2.225–4.434, $p = 0.002$), extrathyroidal extension (OR = 2.204, 95 % CI 1.941–3.843, $p < 0.001$), maximum diameter of nodule (≥ 20 mm) (OR = 3.211, 95 % CI 2.337–4.411, $p < 0.001$), and C-TIRADS score (OR = 1.356, 95 % CI 1.204–1.527, $p < 0.001$) were PTC in independent risk factors for CLNM. The C-TIRADS score of PTC combined with the location, number, size, and ultrasound features of the lesion and the patient's sex and age are important in predicting whether they present with CLNM and provide a reference basis for the clinical formulation of a reasonable surgical treatment plan.

Introduction

Papillary thyroid cancer (PTC) is the most prevalent of all thyroid cancers, accounting for 85–90 % [1]. PTC grows slowly with a good prognosis and a 10-year survival rate of over 90 % [2]. However, approximately 30–90 % of patients with PTC tend to develop cervical lymph node metastasis [3–5] as some studies have found [6, 7], of which central lymph node metastasis (CLNM) is the most common

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site of metastasis in PTC, with a rate of metastasis as high as 24.1 to 64.1 % [8]. Lymph node dissection (LND) is a common surgical technique for patients with a clinically positive lymph node. However, whether to perform prophylactic central neck dissection for clinically-negative lymph node patients remains controversial [9–11]. Unnecessary central neck dissection increases the risk of laryngeal nerve injury. However, ignoring potentially metastatic lymph nodes may require a second surgery, increasing the incidence of complications such as nerve palsy, brachial plexus palsy, cranial nerve injury, coeliac leak, and parathyroid and laryngeal nerve injuries. Therefore, accurate preoperative assessment of lymph node metastases is crucial for designing a rational surgical plan to reduce the local recurrence rate and avoid re-operation.

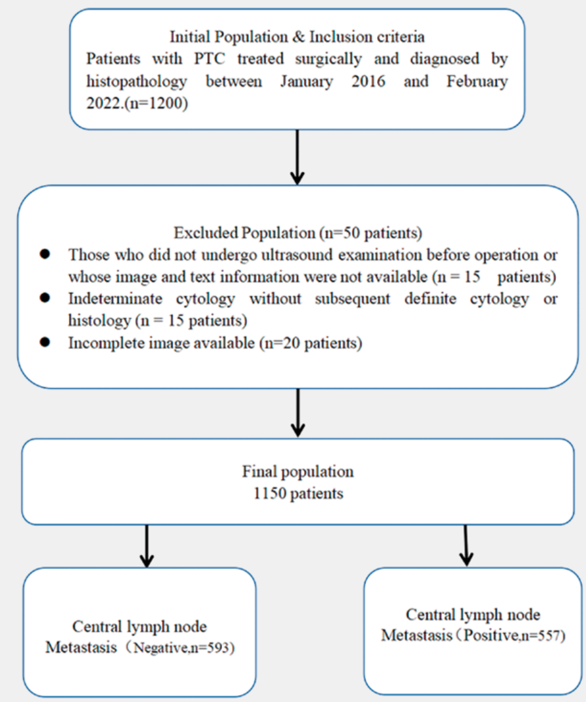
Ultrasonography is an important imaging modality for PTC diagnosis. The thyroid imaging reporting and data system (TI-RADS) [12] points to relevant ultrasound features and uses a cumulative point system of assignment to classify thyroid nodules based on the total score, making the diagnosis of thyroid nodules more objective and easy to operate. In August 2020, Chinese researchers established a practical and simplified Chinese thyroid imaging reporting and data system(C-TIRADS) based on a Chinese patient database [13]. A previous study found that the C-TIRADS score predicts cervical lymph node metastasis in patients with PTC [14] . The detection rate of CLNM by ultrasound is low (10.3–63.63 %) due to the deep location of the central lymph nodes and obscuring by the thyroid gland [15, 16]. Previous studies have found that ultrasound features of PTC have predictive value for CLNM in PTC [17–19].

To improve the detection rate of preoperative lymph node metastasis in patients with PTC and provide a scientific reference basis for clinical diagnosis and preoperative surgery selection, we investigated the relationship between ultrasound features and C-TIRADS scores of PTC and the risk of central lymph node metastasis using a large series of patients with surgically proven PTC.

Patients and Methods

Patients

This retrospective study was approved by the Institutional Review Board of the Foshan First People's Hospital. All the participants provided written informed consent for using their clinical records. A total of 1150 patients with pathologically proven thyroid carcinoma underwent thyroidectomy between January 2016 and February 2022 at Foshan First People's Hospital. There were 351 (30.5 %) males and 799 (69.5 %) females with a mean age of 41.9 ± 12.3 years (range 18–84 years). The inclusion criteria for the patients were as follows: (a) age ≥ 18 years, (b) no previous thyroid surgery, (c) lymph node dissection in the central region, and (d) postoperative pathology of papillary thyroid cancer. The exclusion criteria were as follows: (a) diffuse thyroid changes; (b) history of previous thyroid surgery; no preoperative ultrasound examination or unknown ultrasound graphic data; (c) other concomitant malignant tumours, such as nasopharyngeal carcinoma; and (d) other serious organic diseases, such as cardiac dysfunction (▶ **Fig. 1**).



▶ **Fig 1** Flow chart of patient inclusion.

Methods

Ultrasonographic examination was performed using graphic ultrasound scanners, such as Yum MyLab C, GE Logiq 9, Sequoia S2000, and Esaote MyLab 70, equipped with a high frequency 5e12 MHz linear probe. Clinical information such as the sex and age of the patient was collected, and ultrasound features of thyroid nodules and lymph nodes in the neck were observed and recorded. The risk of malignancy in the thyroid nodules was graded using the C-TIRADS. The ultrasound features of the nodules were recorded according to the C-TIRADS: composition, echogenicity, aspect ratio, margins, and calcification. The final score was summed by scoring the degree of each ultrasound feature to calculate the total score. The ultrasound images were analysed retrospectively by two doctors with more than five years of experience in thyroid diagnosis in a double-blind fashion; in case of disagreement, a consensus diagnosis was obtained through consultation, thus ensuring accurate results.

C-TIRADS classification

The C-TIRADS classification sets vertical, solid, very hypoechoic, punctate strong echogenicity (suspicious for microcalcifications), blurred/irregular margins, or extrathyroidal invasion as ultrasound features of malignant nodules, and comet-tail artefacts as ultrasound features of benign nodules. The number of malignant ultrasound features listed above was counted; one point was scored for each malignant ultrasound feature, and one point was subtracted for the presence of comet-tail artifacts of benign features. Risk stratification of the nodules is based on the total score: –1 for C-TIRADS category 2, 0 for C-TIRADS category 3, 1 for C-TIRADS category

4 A, 2 for C-TIRADS category 4B, 3–4 for C-TIRADS category 4 C, and 5 for C-TIRADS category 5.

Statistical analysis

Statistical analyses were performed using SPSS version 22.0. The measurement data (age, maximum diameter, C-TIRADS score) were expressed as $x \pm s$, and the one-sample Shapiro–Wilk test was used to test the normality of the samples. If the p-value was > 0.05, the data followed normal distribution, and the two-independent samples *t*-test was selected. If the p-value was ≤ 0.05, the data did not follow normal distribution and the non-parametric Mann–Whitney U-test was selected; count data (sex, site, ultrasound characteristics, etc.) were expressed as number of cases and percentage, and the chi-square test was performed. The risk factors for lymph node metastasis in the central region were explored, and variables that were significant in the univariate analysis were included in the multifactorial logistic regression analysis. All results were considered statistically significant at $p < 0.05$.

Results

General characteristics

The study included 1150 patients with postoperative, pathologically confirmed PTC, of whom 799 (69.5 %) were females, and 351 (30.5 %) were males. There were 30.0 % (345/1150) of patients with multifocal PTC (≥ 2 lesions) and 70.0 % (805/1150) of patients with unifocal PTC; 18.0 % (207/1150) of PTC were located in the upper pole, 55.7 % (640/1150) in the middle and 26.3 % (303/1150) in the lower pole. Of the PTCs, 48.4 % (557/1150) had CLNM, and 51.6 % (593/1150) did not. According to the C-TRADS classification, 1.0 % (12/1150) of thyroid nodules were category 3, 7.4 % (85/1150) were category 4 A, 21.3 % (245/1150) were category 4 B, 64.6 % (743/1150) were category 4 C, and 5.7 % (65/1150) were category 5 nodules.

The C-TIRADS score for PTC was 3.0 ± 1.0 and 2.8 ± 1.0 in the CLNM and non-CLNM groups, respectively, and the maximum diameter of the nodules was 17.1 ± 10.8 and 13.3 ± 9.2 in the CLNM and non-CLNM groups, respectively (both p-values < 0.001) (▶ **Table 1**).

▶ **Table 1** Baseline clinicopathological characteristics of 1150 PTC patients.

Clinicopathological properties		n (%)
Gender	Male	351 (30.5)
	Female	799 (69.5)
Age (years)	≤ 45	724 (63.0)
	> 45	426 (37.0)
Multifocality	No	805 (70.0)
	Yes	345 (30.0)
Marker hypo-echogenicity	No	870 (75.7)
	Yes	280 (24.3)
Microcalcification	No	413 (35.9)
	Yes	737 (64.1)
Location of lesion	Upper	207 (18.0)
	Middle	640 (55.7)
	Lower	303 (26.3)
Vertical position	No	606 (52.7)
	Yes	544 (47.3)
Substantial nodules	No	40 (3.5)
	Yes	1110 (96.5)
External invasion	No	764 (66.4)
	Yes	386 (33.6)
C-TIRADS	3	12 (1.0)
	4 A	85 (7.4)
	4B	245 (21.3)
	4 C	743 (64.6)
	5	65 (5.7)
Diameter of the nodule(mm)	≤ 10	527 (45.9)
	10–20	376 (32.7)
	≥ 20	246 (21.4)

Single-factor analysis

The relationship between clinicopathological information and CLNM is shown in ▶ **Table 2**. The location of PTC nodules, maximum diameter of the nodule, microcalcification, margins, whether they were multifocal, and their C-TIRADS classification and score, as well as the patient's sex and age, were statistically significant in the two groups of patients with PTC with and without CLNM (all p-values < *0*.05). In addition, the echogenicity, morphology (vertical), and nature (solid) of the nodules did not differ significantly between the two groups (p-values all > 0.05).

Multivariate logistic regression analysis

Based on the univariate analysis, all factors associated with central cervical lymph node metastasis in PTC were analysed using multivariate logistic regression. Among the predictors, gender (male) (OR = 1.586, 95 % CI 1.232–2.042, p < 0.001), age (≤ 45 years) (OR = 1.508, 95 % C 1.184–1.919, p = 0.001), location of the node (lower pole) (OR = 2.193, 95 % CI 1.519–3.166, p < 0.001), number of lesion (multifocal) (OR = 2.204, 95 % CI 1.227–2.378, p < 0.001), microcalcification (OR = 1.610, 95 % CI 2.225–4.434, p = 0.002), extrathyroidal extension (OR = 2.204, 95 % CI 1.941–3.843, p < 0.001), maximum diameter of nodule (≥ 20 mm) (OR = 3.211, 95 % CI 2.337–4.411, p < 0.001), and C-TIRADS score (OR = 1.356, 95 % CI 1.204–1.527, p < 0.001) were independent risk factors for CLNM in PTC (▶ **Table 3**).

Discussion

Lymph node metastasis(LNM)is very common in PTC patients . Among the lymph nodes, those in the central neck compartment (level VI) have the highest risk of metastasis, which can be as high as 70 % [20]. And CLNM is highly associated with recurrence and overall survival. At present, surgery is still the main treatment for

▶ **Table 2** Ultrasonographic characteristics of PTCs.

Characteristics		The status of metastatic lymph nodes		Statistic (χ^2/t/Z)	p-Value
		Negative (n = 593)	Positive (n = 557)		
Gender	Male	153 (25.8)	198 (35.5)	12.866	< 0.001
	Female	440 (74.2)	359 (64.5)		
Age (years)	≤ 45	346 (58.3)	378 (67.9)	11.153	0.001
	> 45	247 (41.7)	179 (32.1)		
Multifocality	Solitary	465 (78.4)	340 (61.0)	41.283	< 0.001
	Multifocal	128 (21.6)	217 (39.0)		
Marked hypo-echogenicity	Yes	138 (23.3)	142 (25.5)	0.770	0.380
	No	455 (76.7)	415 (74.5)		
Microcalcification	Yes	335 (56.5)	402(72.2)	30.682	< 0.001
	No	258 (43.5)	155 (27.8)		
Location of lesion	Upper	133 (22.4)	74 (13.3)	19.977	< 0.001
	Middle	326 (55.0)	314 (56.4)		
	Lower	134 (22.6)	169 (30.3)		
Substantial nodules	Yes	573 (96.6)	537 (96.4)	0.041	0.840
	No	20 (3.4)	20 (3.6)		
Vertical position	Yes	278 (46.9)	266 (47.8)	0.088	0.766
	No	315 (53.1)	291 (52.2)		
External invasion	No	452 (76.2)	312 (56.0)	52.600	< 0.001
	Yes	141 (23.8)	245 (44.0)		
Maximum diameter of the nodule (mm)	≤ 10	327 (55.2)	200 (35.9)	55.990	< 0.001
	10–20	182 (30.7)	194 (34.8)		
	≥ 20	83(14.0)	163 (29.3)		
C-TIRADS	3	8 (1.3)	4 (0.7)	27.912	< 0.001
	4 A	58 (9.8)	27 (4.8)		
	4B	137 (23.1)	108 (19.4)		
	4 C	372 (62.7)	371 (66.6)		
	5	18 (3.0)	47 (8.4)		
TI-RADS score		2.8 ± 1.0	3.0 ± 1.0	–4.419	< 0.001
Maximum diameter of the nodule (x ± s)		13.3 ± 9.2	17.1 ± 10.8	–7.512	< 0.001

PTCs, and one of the controversial aspects of PTC surgery is whether prophylactic central lymph node dissection is necessary. Preoperative lymph node metastasis assessment helps to design a rational surgical plan and is crucial to reduce local recurrence rates and avoid reoperation. In especially some patients with PTC who have early metastases and lack distinctive features, the presence of CLNM can help determine the surgical plan. Therefore, accurate preoperative evaluation of CLNM provides a more accurate and objective basis for individualised treatment decisions for PTC [21, 22]. Several studies have shown that certain ultrasound features of PTC correlate with CLNM; however, the results of these studies are inconsistent. The results of univariate and multivariate logistic regression analysis in our study showed that the independent risk factors for CLNM in PTC were as follow: male, nodule located in the lower pole, multifocal, microcalcification, extrathyroidal extension, the maximum nodule diameter (≥ 20 mm), high C-TIRADS score and C-TIRADS classification (5 categories).

It has been demonstrated [23] that oestrogen is an agonist in benign and malignant thyroid nodules, which is the reason for the high prevalence of thyroid cancer in women. Still, the incidence of CLNM is higher in men than in female patients [24], possibly because different types of oestrogen receptors are protective factors for PTC [23]. In the CLNM group in our study, males had higher risks of developing CLNM than females (OR = 1.586, 95 % CI 1.232–2.042). Shukla et al.'s [25] study found that lymph node metastases were more likely to occur in younger patients than in older patients. The present study found an increased risk of CLNM at age ≤ 45 years (OR = 1.508, 95 % CI 1.184–1.919), consistent with the findings of Feng et al. [26]. The correlation between tumour location and CLNM remains controversial. In our study,

▶ **Table 3** Multivariate analysis of ultrasonographic characteristics of CLNM from PTCs.

	B	S.E.	Wals	Sig.	Exp (B)	95 % of EXP (B) C.I.
Age (≤45)	0.410	0.123	11.105	0.001	1.508	1.184–1.191
Gender (Male)	0.461	0.129	12.784	<0.001	1.586	1.232–2.042
Location of lesion						
Upper			17.879	<0.001		
Middle	0.548	0.167	10.773	0.001	1.729	1.247–2.398
Lower	0.785	0.187	17.555	<0.001	2.193	1.519–3.166
Multifocality	0.699	0.138	25.788	<0.001	2.204	1.227–2.378
Microcalcification	0.476	0.151	9.903	0.002	1.610	2.225–4.434
External invasion	0.790	0.134	35.006	<0.001	2.204	1.941–3.843
TI-RADS (3)			10.706	0.030		
4 A	–0.189	0.666	0.081	0.766	0.827	0.224–3.054
4B	0.130	0.638	0.042	0.839	1.139	0.326–3.978
4 C	0.067	0.637	0.011	0.916	1.070	0.307–3.730
5	0.938	0.700	1.970	0.126	2.672	0.677–10.535
TI-RADS score	0.304	0.217	51.474	<0.001	1.356	1.204–1.527
Maximum diameter of the nodule (≤10 mm)			54.256	<0.001		
10 mm–20 mm	0.555	0.137	16.495	<0.001	1.743	1.333–2.279
≥20 mm	1.167	0.162	51.859	<0.001	3.211	2.337–4.411

tumours presenting with CLNM were located in the upper pole (13.3 %), middle pole (56.4 %), and lower pole (30.3 %), and the results of data analysis revealed that tumours located in the lower pole had a higher risk of developing CLNM than tumours in other locations, which is consistent with the findings of Mao et al. [27].

Multifocality is an important biological characteristic of papillary thyroid carcinoma, with an incidence ranging from 18 % to 87 % [28, 29]. Multifocal tumours are more malignant and aggressive; previous studies have found multifocality in PTC is also associated with CLNM [30]. Feng et al. [31] the incidence of central lymph node metastasis was higher in patients with multifocal PTC than in those with isolated PTC. In the present study, multifocality was a risk factor for CLNM (OR = 2.204, 95 % CI 1.227–2.378). There is a relationship between tumour lesion size and CLNM, with larger tumours usually being more aggressive [18]; however, the thresholds acquired vary from different studies. Jiang et al. [32] found that tumour size > 5 mm was an independent risk factor for CLNM, whereas Feng et al. [33] found that tumour size > 7.5 mm was significantly associated with CLNM. The results of this study showed that the odds of CLNM were higher for the maximum diameter ≥20 mm of the nodule (OR = 3 .211, 95 % CI 2.337–4.411). Microcalcification, a calcium salt deposit caused by the proliferation of blood vessels and fibrous tissue, is commonly used as a potentially malignant feature on ultrasound [34–36]. Previous studies have reported that CLNM is more likely to occur in PTC with microcalcifications [37]. In this study, 72.2 % (402/557) of the CLNM group and 27.8 % (155/557) of the lesions in the non-CLNM group had microcalcification, which was significantly different ($p < 0.001$), and multivariate analysis indicated that microcalcification was an independent risk factor for CLNM. Therefore, CLNM is more likely to occur if the maximum tumour diameter is ≥20 mm and if it is a multilocal nodule or is accompanied by microcalcification.

Research [38, 39] has found that extrathyroidal extension (ETE) is associated with mortality and recurrence rates in patients with PTC. Feng et al. [19] demonstrated that patients with ETE were 2.144 times more likely to develop CLNM than patients without ETE and suggested that the relationship between ETE and CLNM could provide a theoretical basis for lymph node dissection in patients with PTC. In the present study, ETE was higher in the CLNM group than in the non-CLNM group (48.4 % vs. 40.8 %), and ETE could be an independent risk factor for CLNM, consistent with the results of previous studies [27, 40].

Park et al. [41] found that as the number of malignant ultrasound features of PTC increased, the likelihood of patients developing cervical lymph node metastases increased significantly. The TI-RADS total score is an overall indicator of the ultrasound features of thyroid nodules and is significantly associated with the presence of lymph node metastases in PTC. Our results showed a higher C-TI-RADS score in the CLNM group than in the non-CLNM group (3.0 ± 1.0 vs. 2.8 ± 1.0, $p < 0.001$). Multivariate analysis showed that each 1-point increase in nodal score was associated with a 35.6 % increased risk of CLNM (OR = 1.356, 95 % CI 1.204–1.527), similar to the results previously reported in the literature [42].

This study has some limitations. First, we used retrospective data from a single institution, which may have introduced bias and affected the applicability and generalisability of the results. In the future, we plan to conduct prospective studies to address this issue. Second, the relevant factors we explored are not comprehensive, and future studies should include more thyroid nodule location information and clinical laboratory indicators. Finally, a retrospective analysis does not allow for real-time observation of the ultrasound features of thyroid nodules, which may affect the accuracy of nodule scoring.

Conclusion

The C-TIRADS simplifies the ultrasound malignant risk stratification of thyroid nodules, and the classification is relatively simple, which is convenient for practical application. In summary, male, age ≤ 45 years, nodes located in the lower pole, multifocality, microcalcification, ETE, large nodal diameter, and high C-TIRADS score are independent risk factors for CLNM in PTC. Therefore, for patients with pre-operative risk factors of CLNM, an accurate evaluation of central compartment is needed to find suspicious CLNM. And pCND should be performed in patients with high risk of CLNM.

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Conflict of Interest

The authors declare that they have no conflict of interest.

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Notice

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Erratum

In the above-mentioned article, the authors Weijun Huang and Deli Chen contributed equally. This was corrected in the online version.