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Positive preoperative circulating tumor cells level associated with lymph node metastasis in papillary thyroid carcinoma patients with capsular invasion

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Abstract

Objective Capsular invasion in papillary thyroid cancer(PTC) refers to thyroid cancer penetrating the capsule without attaching to the surrounding tissue. Patients with and without capsular invasion may differ in the likelihood of lymph node metastasis(LNM). The purpose of this study is to study the relationship between circulating tumor cells(CTCs) and LNM in PTC with or without capsular invasion.

Methods The clinical records of patients (age, gender, CTCs, thyroid function, Hashimoto's thyroiditis, lesions number, lesions diameter, capsular invasion, clinical stage, and LNM) were analyzed retrospectively. The relationship between CTCs level and LNM was analyzed. Logistic regression analyses were used to evaluate the relationship between CTCs and LNM after adjusting for confounding factors.

Results A total of 746 PTC patients were included, and 320 patients with capsular invasion and 426 without. The patients with capsular invasion had higher proportions of multifocality, maximum lesion diameter > 1 cm, T3-T4 stage, and LNM than patients without (all $p < 0.05$). In multivariate logistic regression analyses, maximum lesion diameter > 1 cm (odds ratio(OR): 4.108, 95% confidence interval(CI): 2.459–6.862, $p < 0.001$) was associated with LNM in patients without capsular invasion; positive preoperative CTCs levels (OR: 1.705, 95% CI: 1.023–2.842, $p = 0.041$), multifocality (OR: 2.811, 95% CI: 1.669–4.736, $p < 0.001$), and maximum lesion diameter > 1 cm (OR: 3.233, 95% CI: 1.884–5.546, $p < 0.001$) were associated with LNM in patients with capsular invasion.

Conclusions Maximum lesion diameter > 1 cm was associated with LNM in PTC patients with and without capsular invasion. Positive preoperative CTCs levels and multifocality were associated with LNM in patients with capsular invasion, but not in patients without capsular invasion.

Keywords Papillary thyroid carcinoma, Capsular invasion, Circulating tumor cell, Lymph node metastasis

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Introduction

Thyroid cancer is a common malignant tumor of the thyroid gland, and papillary thyroid cancer (PTC) is the most common type of thyroid cancer, accounting for about 80–85% of thyroid malignancies [1]. In recent years, due to a variety of factors, the incidence of thyroid cancer is increasing, which poses a serious threat to national life and health [2]. Factors influencing the prognosis of PTC include age, sex, tumor size, histological findings, capsule invasion, *BRAF* gene variation, lymph node metastasis (LNM), and distant metastasis [3–5]. PTC is considered to be an inert tumor due to its well-differentiated and low malignancy, but its susceptibility to LNM is a factor associated with poor prognosis that cannot be ignored [6–9]. Study has believed that the appearance of metastasis will affect the prognosis of PTC patients, and the mortality of PTC patients with LNM is significantly increased [10].

Invasion is an important factor in the classification, risk stratification and staging of thyroid cancer [11]. The growth mode of malignant tumors is generally expansive growth, continuous growth of cancer cells invading the envelope. Capsular invasion is defined as thyroid cancer penetrating the capsule without attaching to the surrounding tissue [12]. When the capsule loses its integrity, cancer cells invade and metastasis through blood vessels and lymph node channels [13, 14]. Some studies suggest that cervical LNM of thyroid cancer is related to capsular invasion [15–17]. Capsular invasion often indicates malignant proliferation and local invasion of tumors, and is an important risk factor for LNM [18, 19]. However, some studies suggest that capsular invasion may not be the key factor triggering LNM [20]. Patients with and without capsular invasion may differ in the risk of progression and the likelihood of poor prognosis. Therefore, it is of great clinical significance to analyze the risk of LNM in PTC patients with and without capsular invasion, respectively.

The process of tumor metastasis is associated with the aggressiveness of tumor cells [21, 22]. The pathways of tumor metastasis mainly include: hematoinfiltration of primary tumor cells, survival of tumor cells in the blood, distant extravasation, and deposition of tumor cells at metastatic sites [23, 24]. Tumor cells that exist in the blood in free or clustered form are called circulating tumor cells (CTCs) [25]. At present, CTC has been used for early screening, prognosis assessment, and drug sensitivity measurement of tumors due to its advantages of easy access and real-time monitoring [25–27]. Is the levels of CTCs correlated with LNM in PTC with or without capsular invasion? As far as we know, it's still unclear. The purpose of this study is to study the relationship between CTCs and LNM in PTC with or without capsular invasion. It is expected to provide valuable reference data for the role of CTCs in the risk assessment of LNM in PTC with or without capsular invasion.

Materials and methods

Subjects

This study retrospectively analyzed the clinical records of 746 patients with PTC who were hospitalized in Meizhou People's Hospital from June 2021 to April 2023. Inclusion criteria were as follows: (1) histopathological examination confirmed PTC in the patient; (2) patients without other tumors; and (3) medical records were complete. Exclusion criteria were as follows: (1) patients with a history of neck disease and surgery; (2) patients with other types of thyroid cancer or with tumors at other sites; and (3) patients with incomplete medical records. This study was supported by the Ethics Committee of the Meizhou People's Hospital.

Clinical medical records collection

Clinical medical records of the PTC patients were collected, such as age, gender, preoperative CTCs, thyroid function, Hashimoto's thyroiditis, number of tumor lesions, maximum lesion diameter, whether the capsule is invaded, clinical stage, and LNM. According to the age of the patients, they were divided into <55 years old and ≥ 55 years old [28, 29]. The number and size of the tumor lesions were determined by pathological analysis of the thyroid tissue after surgery. The tumor size group was divided into two groups: maximum lesion diameter ≤ 1 cm and >1 cm [5, 30]. The diagnosis of Hashimoto's thyroiditis is based on clinical symptoms, histological features, and radiologic evaluation [31]. The histological features of Hashimoto's thyroiditis were characterized by diffuse lymphocyte and plasma cell infiltration, lymphoid follicular formation, and presence of active germinal centers in the normal area of the thyroid. Ultrasonography of the thyroid in Hashimoto's thyroiditis may indicate diffuse enlargement of the thyroid, reduced echo, gridded or stringy changes, and normal or increased blood flow signals.

According to the guidelines for the diagnosis and management of thyroid disorders [32], the diagnostic criteria for thyroid function are as follows: (1) normal thyroid function is defined as: $0.27\text{mIU/L} \leq$ thyroid stimulating hormone (TSH) $\leq 4.2\text{mIU/L}$, $3.1\text{pmol/L} \leq$ free triiodothyronine (FT3) $\leq 6.8\text{pmol/l}$, $12.0\text{pmol/L} \leq$ free thyroxine (FT4) $\leq 22.0\text{pmol/L}$; (2) hyperthyroidism is defined as TSH $<0.27\text{mIU/L}$; FT4 $>22\text{pmol/L}$ or FT3 $>6.8\text{pmol/L}$; (3) hypothyroidism is defined as TSH $>4.2\text{mIU/L}$ and FT4 $<12\text{pmol/L}$. In this study, hyperthyroidism and hypothyroidism were classified as thyroid dysfunction.

CTCs detection

Three ml of peripheral venous blood was collected from each tester into EDTA-containing test tube from each patient one day before surgery for folate receptor-positive circulating tumor cells (FR + CTCs) analysis. Peripheral blood CTCs were detected by reverse transcription-polymerase chain reaction (RT-PCR) technique using the CytoploRare Kit (Genosaber Biotech, Shanghai, China). Folate receptor Unit (FU) per 3mL (FU/3mL) as defined in the manufacturer's manual, was used to represent the level of FR + CTC in 3 mL of peripheral blood. According to the threshold set in the CTC test kit instructions, CTC ≥ 8.7 FU/3mL is considered to be positive for CTC levels, and CTC < 8.7 FU/3mL is negative.

Table 1 The clinicopathological features of patients with PTC

Clinicopathological features	PTC patients ($n = 746$)
Age (Years)	
< 55, n (%)	612 (82.0%)
≥ 55, n (%)	134 (18.0%)
Gender	
Male, n (%)	140 (18.8%)
Female, n (%)	606 (81.2%)
Thyroid function	
Normal, n (%)	661 (88.6%)
Abnormal, n (%)	85 (11.4%)
Hashimoto's thyroiditis	
No, n (%)	550 (73.7%)
Yes, n (%)	196 (26.3%)
Multifocality	
No, n (%)	528 (70.8%)
Yes, n (%)	218 (29.2%)
Maximum lesion diameter	
≤ 1 cm, n (%)	515 (69.0%)
> 1 cm, n (%)	231 (31.0%)
T stage	
T1-T2, n (%)	683 (91.6%)
T3-T4, n (%)	63 (8.4%)
LNM	
No, n (%)	407 (54.6%)
Yes, n (%)	339 (45.4%)
Preoperative CTCs (FU/3mL)	
Negative (< 8.7)	298 (39.9%)
Positive (≥ 8.7)	448 (60.1%)
Capsular invasion	
No, n (%)	426 (57.1%)
Yes, n (%)	320 (42.9%)
Surgical procedure	
Thyroid lobectomy, n (%)	466 (62.5%)
Thyroidectomy, n (%)	179 (24.0%)
Neck lymph node dissection, n (%)	101 (13.5%)

PTC, papillary thyroid carcinoma; LNM, lymph node metastasis; CTC, circulating tumor cell; FU, folate receptor unit

Statistical analysis

SPSS statistical software (version 26.0, IBM Inc., USA) was used for data analysis. Chi-square test or Fisher's exact test were used to evaluate the relationship between capsular invasion and clinical features; compare the relationship between clinicopathological features and LNM in patients with and without capsular invasion. Univariate and multivariate logistic regression analyses (age, gender, thyroid function, Hashimoto's thyroiditis, multifocality, maximum lesion diameter, and clinical stage were selected as covariates) were used to evaluate the relationship between CTCs and LNM in PTC patients with and without capsular invasion, based on estimating the odds ratios (OR) and their 95% confidence intervals (CIs). $p < 0.05$ was set as statistically significant.

Results

Clinicopathological features of patients with PTC

A total of 746 patients with PTC were included in this study. There were 612 (82.0%) cases with < 55 years old and 134 (18.0%) cases with ≥ 55 years old; and 140 (18.8%) are male and 606 (81.2%) are female in these patients. There were 85 (11.4%), 196 (26.3%), 218 (29.2%), 231 (31.0%), and 320 (42.9%) patients with abnormal thyroid function, Hashimoto's thyroiditis, multifocality, maximum lesion diameter > 1 cm, and capsular invasion, respectively. There were 339 (45.4%) and 448 (60.1%) patients with LNM and positive preoperative CTCs (≥ 8.7 FU/3mL), respectively. In this study, 466 (62.5%), 179 (24.0%), and 101 (13.5%) patients underwent thyroid lobectomy, thyroidectomy, and neck lymph node dissection, respectively (Table 1).

Comparison of clinicopathological features in PTC patients with and without capsular invasion

The PTC patients with capsular invasion had higher proportions of multifocality (39.4% vs. 21.6%, $p < 0.001$), maximum lesion diameter > 1 cm (45.6% vs. 20.0%, $p < 0.001$), T3-T4 stage (18.4% vs. 0.9%, $p < 0.001$), and LNM (57.8% vs. 36.2%, $p < 0.001$) than patients without capsular invasion. There was no statistically significant difference in age, gender, thyroid function, Hashimoto's thyroiditis, and preoperative CTCs levels between patients with and without capsular invasion (Table 2).

Comparison of clinicopathological features between PTC with and without LNM in patients without capsular invasion

In PTC patients without capsular invasion ($n = 426$), there were 272 (272/426, 63.8%) and 154 (154/426, 36.2%) patients without and with LNM, respectively. The patients with LNM had higher proportions of multifocality (27.9% vs. 18.0%, $p = 0.020$), and maximum lesion diameter > 1 cm (35.7% vs. 11.0%, $p < 0.001$) than patients

Table 2 Comparison of clinicopathological features in PTC patients with and without capsular invasion

Clinicopathological features	Capsular invasion		*p*values
	No (*n* = 426)	Yes (*n* = 320)	
Age (Years)			
< 55, n (%)	349(81.9%)	263(82.2%)	1.000
≥ 55, n (%)	77(18.1%)	57(17.8%)	
Gender			
Male, n (%)	83(19.5%)	57(17.8%)	0.571
Female, n (%)	343(80.5%)	263(82.2%)	
Thyroid function			
Normal, n (%)	371(87.1%)	290(90.6%)	0.162
Abnormal, n (%)	55(12.9%)	30(9.4%)	
Hashimoto's thyroiditis			
No, n (%)	319(74.9%)	231(72.2%)	0.449
Yes, n (%)	107(25.1%)	89(27.8%)	
Multifocality			
No, n (%)	334(78.4%)	194(60.6%)	< 0.001
Yes, n (%)	92(21.6%)	126(39.4%)	
Maximum lesion diameter			
≤ 1 cm, n (%)	341(80.0%)	174(54.4%)	< 0.001
> 1 cm, n (%)	85(20.0%)	146(45.6%)	
T stage			
T1-T2, n (%)	422(99.1%)	261(81.6%)	< 0.001
T3-T4, n (%)	4(0.9%)	59(18.4%)	
LNM			
No, n (%)	272(63.8%)	135(42.2%)	< 0.001
Yes, n (%)	154(36.2%)	185(57.8%)	
Preoperative CTCs (FU/3mL)			
Negative (< 8.7)	169(39.7%)	129(40.3%)	0.880
Positive (≥ 8.7)	257(60.3%)	191(59.7%)	

PTC, papillary thyroid carcinoma; CTC, circulating tumor cell; FU, folate receptor unit

without LNM. There was no statistically significant difference in age, gender, thyroid function, Hashimoto's thyroiditis, T stage, and preoperative CTCs levels between patients without and with LNM (Table 3).

Comparison of clinicopathological features between PTC with and without LNM in patients with capsular invasion

In PTC patients with capsular invasion ($n = 320$), there were 135 (135/320, 42.2%) and 185 (185/320, 57.8%) patients without and with LNM, respectively. The patients with LNM had higher proportions of multifocality (49.2% vs. 25.9%, $p < 0.001$), maximum lesion diameter > 1 cm (58.9% vs. 27.4%, $p < 0.001$), T3-T4 stage (24.9% vs. 9.6%, $p = 0.001$), and positive preoperative CTCs levels (65.4% vs. 51.9%, $p = 0.016$) than patients without LNM. There was no statistically significant difference in age, gender, thyroid function, and Hashimoto's thyroiditis between patients without and with LNM (Table 4).

Logistic regression analysis of risk factors of LNM in PTC with and without capsular invasion

In PTC patients without capsular invasion, multifocality (odds ratio (OR): 1.763, 95% confidence interval (CI): 1.103–2.817, $p = 0.018$), and maximum lesion diameter > 1 cm (OR: 4.481, 95% CI: 2.711–7.408, $p < 0.001$) were associated with LNM in univariate analysis. Maximum lesion diameter > 1 cm (OR: 4.108, 95% CI: 2.459–6.862, $p < 0.001$) was associated with LNM in multivariate analysis (Table 5).

In PTC patients with capsular invasion, positive preoperative CTCs levels (OR: 1.756, 95% CI: 1.115–2.763, $p = 0.015$), multifocality (OR: 2.766, 95% CI: 1.710–4.474, $p < 0.001$), maximum lesion diameter > 1 cm (OR: 3.799, 95% CI: 2.354–6.129, $p < 0.001$), and T3-T4 stage (OR: 3.106, 95% CI: 1.602–6.020, $p = 0.001$) were associated with LNM in univariate analysis. Positive preoperative CTCs levels (OR: 1.705, 95% CI: 1.023–2.842, $p = 0.041$), multifocality (OR: 2.811, 95% CI: 1.669–4.736, $p < 0.001$), and maximum lesion diameter > 1 cm (OR: 3.233, 95% CI: 1.884–5.546, $p < 0.001$) were associated with LNM in multivariate analysis (Table 5).

Discussion

Most studies suggest that capsular invasion was a risk factor for LNM in PTC patients [33–35]. There may be differences in the likelihood of LNM in patients with and

Table 3 Comparison of clinicopathological features between PTC with and without LNM in patients without capsular invasion

Clinicopathological features	Non-LNM ($n=272$)	LNM ($n=154$)	*p*values
Age (Years)			
< 55, n (%)	220(80.9%)	129(83.8%)	0.513
≥ 55, n (%)	52(19.1%)	25(16.2%)	
Gender			
Male, n (%)	45(16.5%)	38(24.7%)	0.056
Female, n (%)	227(83.5%)	116(75.3%)	
Thyroid function			
Normal, n (%)	232(85.3%)	139(90.3%)	0.176
Abnormal, n (%)	40(14.7%)	15(9.7%)	
Hashimoto's thyroiditis			
No, n (%)	200(73.5%)	119(77.3%)	0.418
Yes, n (%)	72(26.5%)	35(22.7%)	
Multifocality			
No, n (%)	223(82.0%)	111(72.1%)	0.020
Yes, n (%)	49(18.0%)	43(27.9%)	
Maximum lesion diameter			
≤ 1 cm, n (%)	242(89.0%)	99(64.3%)	< 0.001
> 1 cm, n (%)	30(11.0%)	55(35.7%)	
T stage			
T1-T2, n (%)	271(99.6%)	151(98.1%)	0.137
T3-T4, n (%)	1(0.4%)	3(1.9%)	
Preoperative CTCs (FU/3mL)			
Negative (< 8.7)	112(41.2%)	57(37.0%)	0.411
Positive (≥ 8.7)	160(58.8%)	97(63.0%)	

PTC, papillary thyroid carcinoma; LNM, lymph node metastasis; CTC, circulating tumor cell

Table 4 Comparison of clinicopathological features between PTC with and without LNM in patients with capsular invasion

Clinicopathological features	Non-LNM ($n=135$)	LNM ($n=185$)	*p*values
Age (Years)			
< 55, n (%)	107(79.3%)	156(84.3%)	0.300
≥ 55, n (%)	28(20.7%)	29(15.7%)	
Gender			
Male, n (%)	22(16.3%)	35(18.9%)	0.559
Female, n (%)	113(83.7%)	150(81.1%)	
Thyroid function			
Normal, n (%)	117(86.7%)	173(93.5%)	0.051
Abnormal, n (%)	18(13.3%)	12(6.5%)	
Hashimoto's thyroiditis			
No, n (%)	101(74.8%)	130(70.3%)	0.380
Yes, n (%)	34(25.2%)	55(29.7%)	
Multifocality			
No, n (%)	100(74.1%)	94(50.8%)	< 0.001
Yes, n (%)	35(25.9%)	91(49.2%)	
Maximum lesion diameter			
≤ 1 cm, n (%)	98(72.6%)	76(41.1%)	< 0.001
> 1 cm, n (%)	37(27.4%)	109(58.9%)	
T stage			
T1-T2, n (%)	122(90.4%)	139(75.1%)	0.001
T3-T4, n (%)	13(9.6%)	46(24.9%)	
Preoperative CTCs (FU/3mL)			
Negative (< 8.7)	65(48.1%)	64(34.6%)	0.016
Positive (≥ 8.7)	70(51.9%)	121(65.4%)	

PTC, papillary thyroid carcinoma; LNM, lymph node metastasis; CTC, circulating tumor cell

Table 5 Logistic regression analysis of risk factors of LNM in PTC with and without capsular invasion

Variables	No capsular invasion				Capsular invasion			
	Univariate		Multivariate		Univariate		Multivariate	
	OR (95% CI)	*p* values	OR (95% CI)	*p* values	OR (95% CI)	*p* values	OR (95% CI)	*p* values
Preoperative CTCs (≥8.7/<8.7, FU/3mL)	1.191 (0.793–1.789)	0.399	1.073 (0.693–1.664)	0.751	1.756 (1.115–2.763)	0.015	1.705 (1.023–2.842)	0.041
Age (<55/≥55, years old)	1.220 (0.722–2.060)	0.458	1.269 (0.721–2.234)	0.409	1.408 (0.792–2.501)	0.243	1.250 (0.655–2.384)	0.498
Gender (male/female)	1.652 (1.016–2.687)	0.043	1.649 (0.972–2.799)	0.064	1.198 (0.667–2.154)	0.545	0.922 (0.480–1.771)	0.807
Thyroid function (abnormal/normal)	0.626 (0.334–1.175)	0.145	0.663 (0.339–1.295)	0.229	0.451 (0.209–0.971)	0.042	0.386 (0.163–0.913)	0.030
Hashimoto's thyroiditis (yes/no)	0.817 (0.514–1.298)	0.392	0.828 (0.502–1.366)	0.460	1.257 (0.762–2.073)	0.371	1.008 (0.574–1.772)	0.977
Multifocality (yes/no)	1.763 (1.103–2.817)	0.018	1.571 (0.951–2.596)	0.078	2.766 (1.710–4.474)	<0.001	2.811 (1.669–4.736)	<0.001
Maximum lesion diameter (>1 cm/≤1 cm)	4.481 (2.711–7.408)	<0.001	4.108 (2.459–6.862)	<0.001	3.799 (2.354–6.129)	<0.001	3.233 (1.884–5.546)	<0.001
T stage (T3-T4/T1-T2)	5.384 (0.555–52.214)	0.146	4.595 (0.422–49.993)	0.210	3.106 (1.602–6.020)	0.001	1.916 (0.905–4.058)	0.089

PTC, papillary thyroid carcinoma; LNM, lymph node metastasis; CTC, circulating tumor cell; FU, folate receptor unit; OR, odds ratio; CI, confidence interval

without capsular invasion. Specifically, patients with capsular invasion may not have LNM, while patients without capsular invasion may also have LNM. Therefore, it is worth investigating whether and how there are differences in the risk factors for LNM in patients with and without capsular invasion. However, there has been a lack of reports. This study has studied this problem. The results of this study showed that maximum lesion diameter > 1 cm was associated with LNM in PTC patients with and without capsular invasion; positive preoperative CTCs levels, and multifocality were associated with LNM in PTC patients with capsular invasion, but not in patients without capsular invasion.

In the era of precision medicine, liquid biopsy technology, including CTC, has received more and more attention [36, 37]. CTCs are considered as potential markers for the diagnosis [38], prognosis [39, 40], and distant metastasis [41] of thyroid cancer. Yu et al. revealed that CTCs were associated with LNM in PTC < 1 cm [42]. However, the relationship between CTC and LNM in patients with and without capsular invasion remains unclear. The results of this study suggested that positive preoperative CTCs level was associated with LNM in PTC patients with capsular invasion, but not in patients without capsular invasion. It enriches the data on the evaluation value of CTC in the diagnosis and treatment of thyroid cancer.

Multifocality was significantly associated with LNM in PTC [43–45]. Yang et al. found that multifocality was associated with central lymph node metastasis (CLNM) in patients without capsular invasion [46]. In this study, multifocality was associated with LNM in PTC patients with capsular invasion, but not in patients without capsular invasion. The reason for the inconsistent results may be due to the difference in the sample size of the studies. Therefore, the determination of these inconsistent results requires more researches to reveal. Moreover, some studies have suggested that large tumor diameter was a risk factor of LNM in PTC patients [47–49]. But the lesion diameter division varies from study to study, such as 0.6 cm [50], 0.855 cm [51], 1 cm [29], and 4 cm [52]. There is little research in the relationship between lesion diameter and LNM in patients with and without capsular invasion. In this study, lesion diameter was associated with LNM in PTC patients with and without capsular invasion. Our results are consistent with previous researches [46].

Moreover, thyroid function is closely related to the risk of LNM of thyroid cancer. Zou et al. found that the combination of quantitative parameters and thyroid function indicators (serum thyroglobulin (Tg) and thyroglobulin antibody (TgAb)) predicts the risk of LNM in PTC patients [53]. Some studies revealed that positive Tg [54] and TgAb [54–56] were independent risk factors for LNM in PTC patients. Wen et al. found that thyroid peroxidase antibody (TPOAb) and TgAb double negative and double positive were independent risk factors for LNM [57]. Conversely, individual studies have found that TPOAb levels were inversely associated with the risk of LNM [56]. Another study has found that there was a significant association between TSH level and LNM of thyroid cancer: high TSH was a risk factor for LNM [58]. In addition, a study have found that PTC patients with reduced thyroid hormone sensitivity have a higher risk of developing LNM [59]. Lou et al. believed that the incidence of hypothyroidism in PTC patients with central

LNM was significantly higher than that in PTC patients without central LNM [60], which also explained the relationship between LNM and thyroid function from another aspect. In clinical practice, attention should be paid to the application of thyroid function testing in the diagnosis and treatment of thyroid cancer in order to achieve more accurate individualized treatment. This study found that abnormal thyroid function may be a protective factor for the development of LNM in PTC patients with capsular invasion. Of course, the relationship between thyroid function and LNM still needs more researches to reveal.

In addition, some studies have suggested that younger age was a risk factor of LNM in PTC patients [28, 29, 44, 61, 62]. But the age division varies from study to study, such as 30 [63], 40 [44], 45 [62, 64], 50 [65], and 55 [28, 29] years old. On the contrary, a few studies have suggested that older age was a risk factor of LNM in PTC [66, 67]; and another study found that age was not associated with LNM [68]. As for the relationship between age and LNM in patients with and without capsular invasion, Yang et al. found that age < 55 years old and male were associated with LNM in patients without capsular invasion [46]. But this study did not get similar results. In addition, the occurrence of PTC is different between male and female, with the incidence of women is significantly higher than that of men [69]. However, male patients are more likely to have LNM [70–73]. In this study, the relationship between gender and LNM was not found in patients with and without capsular invasion.

Fine needle aspiration (FNA) and frozen section are commonly used techniques in the diagnosis of thyroid nodules and play an important role in the diagnosis and prognosis assessment of thyroid cancer [74, 75]. However, since FNA may have false-negative results and frozen sections may be misdiagnosed due to time constraints, other techniques and markers are needed to assist in the diagnosis and evaluation of thyroid cancer. The findings of this study suggest that comprehensive consideration of preoperative CTCs level and clinicopathological features (maximum lesion diameter and multifocality) can predict whether there is LNM in PTC patients with capsular invasion. The results of this study provide valuable reference information for the prediction of lymph node metastasis in PTC patients with capsular invasion.

There are some shortcomings in present study. First, it is a single-center retrospective study with limited sample size, and the research results are inevitably biased, which needs to be confirmed by multi-center and large-sample studies. Second, at present, there is no standard method for the detection of CTCs and the evaluation of its level. This study is limited by the efficacy of CTC detection method, and the results of this study may be biased, so the results of this study need more research to confirm. Third, this study only divided patients into those with or without capsular invasion, and did not classify and analyze the degree of capsular invasion of patients with capsular invasion, which may be more clinically significant.

Conclusions

Maximum lesion diameter > 1 cm was associated with LNM in PTC patients with and without capsular invasion. Positive preoperative CTCs levels, and multifocality were associated with LNM in PTC patients with capsular invasion, but not in patients without capsular invasion. In other words, those with positive preoperative CTC levels, tumor diameter > 1 cm, and multifocality have more likelihood to develop LNM in PTC patients with capsular invasion. It provides valuable reference data for the risk assessment of LNM in patients with capsular invasion.

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Author contributions
Ming Yu, Yeqian Lai, and Zhijuan Zheng contributed to study concept and design. Ming Yu, Jiaqin Deng, Yihua Gu, Yeqian Lai, and Zhijuan Zheng collected clinical data. Ming Yu, and Zhijuan Zheng contributed to analyze the data. Ming Yu contributed to prepare the manuscript. All authors approved the final version to be published.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
This study was conducted according to the Declaration of Helsinki and approved by the Human Ethics Committees of Meizhou People's Hospital.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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