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ORIGINAL RESEARCH

Different Risk Factors for Lymph Node Metastasis in Papillary Thyroid Carcinoma Patients with and without Hashimoto's Thyroiditis

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Objective: The immune response triggered by Hashimoto's thyroiditis may influence the progression of papillary thyroid cancer (PTC), such as lymph node metastasis (LNM). The purpose of this study was to study the relationship between clinicopathological features and LNM in PTC patients with and without Hashimoto's thyroiditis.

Methods: The clinicopathological features of 767 PTC patients (age, gender, thyroid function, Hashimoto's thyroiditis, number of tumor lesions, tumor size, capsular invasion, preoperative circulating tumor cells (CTCs), and clinical stage) were collected. The relationship between clinicopathological features and LNM in PTC coexistent and non-coexistent with Hashimoto's thyroiditis patients was analyzed, respectively.

Results: There were 210 PTC patients with Hashimoto's thyroiditis and 557 without. There was no significant difference in clinicopathological features between patients with and without Hashimoto's thyroiditis. In multivariate logistic regression analyses, multifocality (odds ratio (OR): 2.127, 95% confidence interval (CI): 1.085–4.168, p=0.028), maximum lesion diameter >1cm (OR: 3.858, 95% CI: 1.903–7.823, p<0.001), and capsular invasion (OR: 2.007, 95% CI: 1.034–3.895, p=0.040) were associated with LNM in PTC patients with Hashimoto's thyroiditis; multifocality (OR: 2.461, 95% CI: 1.595–3.797, p<0.001), maximum lesion diameter >1cm (OR: 4.108, 95% CI: 2.629–6.417, p<0.001), capsular invasion (OR: 1.680, 95% CI: 1.128–2.500, p=0.011), and positive preoperative CTCs (OR: 1.560, 95% CI: 1.065–2.285, p=0.022) were associated with LNM in PTC patients without Hashimoto's thyroiditis.

Conclusion: Regardless of the presence or absence of Hashimoto's thyroiditis, multifocality, maximum lesion diameter >1cm, and capsular invasion were associated with LNM in PTC patients. Positive preoperative CTCs were associated with LNM in PTC without Hashimoto's thyroiditis but not in PTC with Hashimoto's thyroiditis.

Keywords: papillary thyroid carcinoma, hashimoto's thyroiditis, lymph node metastasis, circulating tumor cell

Introduction

Thyroid cancer is a malignant tumor of the thyroid gland that originates from thyroid epithelial cells.[1] According to the latest statistics released by an international authoritative institution, thyroid cancer has become the fifth most common cancer in women globally.[2] Thyroid cancer is one of the fastest growing malignant tumors in China and is one of the most common malignant tumors with the highest incidence in the Chinese population.[3] Papillary thyroid cancer (PTC) is the most common type of thyroid cancer, which grows relatively slowly and has a good prognosis.[4] Hashimoto's thyroiditis is a chronic immune thyroiditis that uses one's own thyroid tissue as an antigen.[5] The main mechanism of Hashimoto's thyroiditis is that the immune system mistakenly attacks the thyroid tissue, leading to a large number of lymphocyte infiltrates in the thyroid gland, which leads to the destruction of the thyroid follicular structure and the gradual decline of thyroid function.[6,7] According to statistics, its incidence of Hashimoto's thyroiditis in the general population is about 1%–2%, and the incidence in the female population can reach 4 times that of men.[8]

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The relationship between Hashimoto's thyroiditis and thyroid cancer has attracted much attention. Some studies have found that people with Hashimoto's thyroiditis have an increased risk of thyroid cancer compared to the general population.[9,10] The reason may be related to the chronic inflammatory microenvironment caused by Hashimoto thyroiditis. Continuous inflammatory stimulation causes thyroid epithelial cells to proliferate and mutate genes, increasing the likelihood of cancer.[11] On the other hand, it has been suggested that the immune response triggered by Hashimoto's thyroiditis may inhibit the progression of thyroid cancer to a certain extent.[12,13] While the immune system attacks the thyroid tissue, it may also produce immune surveillance and killing effects on early cancer cells.[14] However, at present, the exact relationship between the two is not completely clear, and more research is still needed to further explore.

PTC is prone to lymph node metastasis (LNM) and its adverse effect on prognosis is one of the problems that need to be solved urgently.[15–18] LNM affects the prognosis of PTC patients, and the prognosis of PTC patients with LNM is significantly worse.[19] It is important to determine whether there are differences in risk factors for LNM in PTC patients with and without Hashimoto's thyroiditis. In terms of diagnosis, if the risk of LNM in PTC with and without Hashimoto's thyroiditis can be accurately determined, it will help to optimize the diagnostic process. For patients with high risk of LNM in PTC, lymph node dissection may be more active during surgery to reduce the postoperative recurrence rate. On the contrary, for low-risk patients, excessive lymph node dissection can be avoided, surgical complications can be reduced, and the quality of life of patients can be improved.[20] The purpose of this study is to study the relationship between clinicopathological features and LNM in PTC patients with and without Hashimoto's thyroiditis.

Materials and Methods

Subjects

The clinical medical records of 767 PTC patients diagnosed and treated in Meizhou People's Hospital from June 2021 to April 2023 were collected. Inclusion criteria were as follows: (1) patients with clinical diagnosis of PTC; (2) patients underwent surgical treatment in our hospital; and (3) medical records were complete. Exclusion criteria were as follows: (1) patients with a previous history of thyroid surgery or neck surgery; (2) patients with other tumors other than PTC; (3) patients who did not undergo PTC surgery but received treatments such as radioactive iodine therapy, thyroid stimulating hormone suppression therapy, and targeted therapy; and (4) patients with incomplete medical records. This study was supported by the Ethics Committee of the Meizhou People's Hospital.

Data Collection

All the surgeries in this study were carried out by the same medical team from the Department of thyroid surgery of our hospital. Before the operation, the team held a collective discussion to formulate the surgical plan, clearly defining the extent of thyroid resection and the area for lymph node dissection. The operation was carried out in accordance with the operating procedures. The surgical specimens were handled by specially designated personnel, and all information regarding the tumor location, size, quantity, capsular invasion, and whether it had invaded surrounding tissues was meticulously recorded. The pathological examination was evaluated by two senior pathologists in a double-blind manner. Clinical data of the PTC patients was collected: age, gender, thyroid function, Hashimoto's thyroiditis, number of tumor lesions, maximum lesion diameter, capsular invasion, preoperative circulating tumor cell (CTC), clinical stage, and LNM.

The patients were divided into <55 years old and ≥55 years old based on the age of patients[21,22] maximum lesion diameter ≤1cm and >1cm based on the tumor size.[23,24] The diagnosis of Hashimoto's thyroiditis is the result of a comprehensive evaluation by the clinician based on clinical symptoms (fatigue, cold intolerance, weight gain, constipation, bradycardia), histological features, and radiological findings.[25] The diagnostic criteria of Hashimoto's thyroiditis are as follows: (1) diffuse goiter with a relatively firm texture; (2) positive serum anti-thyroid peroxidase antibodies (TPOAb) and anti-thyroglobulin antibodies (TgAb); (3) enlargement of the isthmus vertebrae; and (4) accompanied by clinical hypothyroidism or subclinical hypothyroidism. In Hashimoto's thyroiditis, ultrasonography examination shows a heterogeneous echotexture and the presence of diffuse hypoechogenicity.[26]

Based on the histopathological examination of Hashimoto's thyroiditis, there is destruction of thyroid follicular epithelial cells, lymphocyte infiltration, plasma cell infiltration, formation of lymphoid follicles and the existence of active germinal centers.[25] In this study, hyperthyroidism and hypothyroidism were classified as thyroid dysfunction.[27]

Venous blood of the patients were collected for the analysis of folate receptor-positive circulating tumor cells (FR+CTCs) using the CytoploRare Kit (Genosaber Biotech, Shanghai, China). Red blood cells were lysed and removed, and folate receptor-positive cells were isolated and enriched using folic acid modified immunomagnetic beads to obtain folate receptor-positive cells. Specific small molecule probes were used to label the folate receptor-positive cells. The oligonucleotides in folate receptor binding small molecule probes were quantitatively detected with polymerase chain reaction (PCR) method using specific primers and Taqman fluorescent probes corresponding to small molecule probes. According to the instructions of the test kit used, CTC≥8.7 FU/3mL (folate receptor Unit per 3mL) is defined as CTC-positive, and CTC <8.7 FU/3mL is defined as negative.

Statistical Analysis

SPSS statistical software (version 26.0) was used for data analysis. Chi-square test or Fisher's exact test were used to evaluate the differences in clinical characteristics between PTC patients with and without Hashimoto's thyroiditis, and analyze the relationship between clinicopathological features and LNM in PTC patients with and without Hashimoto's thyroiditis, respectively. Logistic regression analyses (age, gender, thyroid function, multifocality, maximum lesion diameter, capsular invasion, and clinical stage, and preoperative CTCs as variables) were used to evaluate the risk factors of LNM in PTC patients with and without Hashimoto's thyroiditis, respectively. $p<0.05$ was set as statistically significant.

Results

Clinical Features of PTC Patients

There were 635 (82.8%) with <55 years old and 132 (17.2%) patients aged ≥55; and there were 152 (19.8%) male patients and 615 (80.2%) female patients. There were 210 (27.4%), 86 (11.2%), 214 (27.9%), 233 (30.4%), and 329 (42.9%) patients had Hashimoto's thyroiditis, abnormal thyroid function, multifocality, maximum lesion diameter >1cm, and capsular invasion, respectively. There were 352 (45.9%) and 456 (59.5%) patients had LNM and positive preoperative CTCs (≥8.7 FU/3mL), respectively (Table 1).

Table 1 The Clinicopathological Features of Patients with PTC and Comparison of Clinicopathological Features in Patients with and without Hashimoto's Thyroiditis

Clinicopathological Features	PTC Patients (n=767)	Hashimoto's Thyroiditis		*p* (χ^2)
		No (n=557)	Yes (n=210)	
Age (Years)				
<55, n (%)	635 (82.8%)	458(82.2%)	177(84.3%)	0.522
≥55, n (%)	132 (17.2%)	99(17.8%)	33(15.7%)	(χ^2=0.454)
Gender				
Male, n (%)	152 (19.8%)	129(23.2%)	23(11.0%)	<0.001
Female, n (%)	615 (80.2%)	428(76.8%)	187(89.0%)	(χ^2=14.302)
Hashimoto's thyroiditis				
No, n (%)	557 (72.6%)	–	–	–
Yes, n (%)	210 (27.4%)	–	–	
Thyroid function				
Normal, n (%)	681 (88.8%)	498(89.4%)	183(87.1%)	0.441
Abnormal, n (%)	86 (11.2%)	59(10.6%)	27(12.9%)	(χ^2=0.786)

(*Continued*)

Table 1 (Continued).

Clinicopathological Features	PTC Patients (n=767)	Hashimoto's Thyroiditis		*p* (χ^2)
		No (n=557)	Yes (n=210)	
Multifocality				
No, n (%)	553 (72.1%)	411(73.8%)	142(67.6%)	0.104
Yes, n (%)	214 (27.9%)	146(26.2%)	68(32.4%)	(χ^2=2.885)
Maximum lesion diameter				
≤1cm, n (%)	534 (69.6%)	395(70.9%)	139(66.2%)	0.218
>1cm, n (%)	233 (30.4%)	162(29.1%)	71(33.8%)	(χ^2=1.610)
Capsular invasion				
No, n (%)	438 (57.1%)	322(57.8%)	116(55.2%)	0.567
Yes, n (%)	329 (42.9%)	235(42.2%)	94(44.8%)	(χ^2=0.412)
T stage				
T1-T2, n (%)	703 (91.7%)	514(92.3%)	189(90.0%)	0.380
T3-T4, n (%)	64 (8.3%)	43(7.7%)	21(10.0%)	(χ^2=1.037)
Lymph node metastasis (LNM)				
No, n (%)	415 (54.1%)	298(53.5%)	117(55.7%)	0.626
Yes, n (%)	352 (45.9%)	259(46.5%)	93(44.3%)	(χ^2=0.301)
Preoperative CTCs (FU/3mL)				
Negative (<8.7)	311 (40.5%)	235(42.2%)	76(36.2%)	0.138
Positive (≥8.7)	456 (59.5%)	322(57.8%)	134(63.8%)	(χ^2=2.277)

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

Comparison of Clinical Features in PTC Coexistent and Non-Coexistent with Hashimoto's Thyroiditis Patients

The PTC complicated with Hashimoto's thyroiditis patients had higher proportion of female (89.0% vs 76.8%, χ^2=14.302, p<0.001) than patients without Hashimoto's thyroiditis. There was no statistically significant difference in age, thyroid function, Hashimoto's thyroiditis, multifocality, tumor size, capsular invasion, T stage, LNM, and preoperative CTCs levels between patients with and without Hashimoto's thyroiditis (Table 1).

Comparison of Clinical Features Between PTC with and without LNM in Patients Non-Coexistent with Hashimoto's Thyroiditis

In the 557 PTC patients without Hashimoto's thyroiditis, 298 (298/557, 53.5%) patients had no LNM and 259 (259/557, 46.5%) patients had LNM, respectively. The patients with LNM had higher proportions of male (27.8% vs 19.1%, χ^2=5.855, p=0.016), multifocality (36.7% vs 17.1%, χ^2=27.426, p<0.001), maximum lesion diameter >1cm (46.3% vs 14.1%, χ^2=69.823, p<0.001), capsular invasion (54.1% vs 31.9%, χ^2=27.936, p<0.001), stage T3-T4 (13.1% vs 3.0%, χ^2=19.870, p<0.001), and positive preoperative CTCs levels (63.3% vs 53.0%, χ^2=6.028, p=0.016) than patients without LNM (Table 2).

Table 2 Comparison of Clinicopathological Features Between PTC with and without LNM in Patients without Hashimoto's Thyroiditis

Clinicopathological Features	Non-LNM (n=298)	LNM (n=259)	*p* (χ^2)
Age (Years)			
<55, n (%)	242(81.2%)	216(83.4%)	0.508
≥55, n (%)	56(18.8%)	43(16.6%)	(χ^2=0.455)
Gender			
Male, n (%)	57(19.1%)	72(27.8%)	0.016
Female, n (%)	241(80.9%)	187(72.2%)	(χ^2=5.855)

(*Continued*)

Table 2 (Continued).

Clinicopathological Features	Non-LNM (n=298)	LNM (n=259)	*p* (χ^2)
Thyroid function			
Normal, n (%)	258(86.6%)	240(92.7%)	0.027
Abnormal, n (%)	40(13.4%)	19(7.3%)	(χ^2=5.421)
Multifocality			
No, n (%)	247(82.9%)	164(63.3%)	<0.001
Yes, n (%)	51(17.1%)	95(36.7%)	(χ^2=27.426)
Maximum lesion diameter			
≤1cm, n (%)	256(85.9%)	139(53.7%)	<0.001
>1cm, n (%)	42(14.1%)	120(46.3%)	(χ^2=69.823)
Capsular invasion			
No, n (%)	203(68.1%)	119(45.9%)	<0.001
Yes, n (%)	95(31.9%)	140(54.1%)	(χ^2=27.936)
T stage			
T1-T2, n (%)	289(97.0%)	225(86.9%)	<0.001
T3-T4, n (%)	9(3.0%)	34(13.1%)	(χ^2=19.870)
Preoperative CTCs (FU/3mL)			
Negative (<8.7)	140(47.0%)	95(36.7%)	0.016
Positive (≥8.7)	158(53.0%)	164(63.3%)	(χ^2=6.028)

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

Comparison of Clinical Features Between PTC with and without LNM in Patients Coexistent with Hashimoto's Thyroiditis

In the 210 PTC patients with Hashimoto's thyroiditis, 117 (117/210, 55.7%) patients had no LNM and 93 (93/210, 44.3%) patients had LNM, respectively. The patients with LNM had higher multifocality (46.2% vs 21.4%, χ^2=14.636, p<0.001), tumor size >1cm (54.8% vs 17.1%, χ^2=32.986, p<0.001), capsular invasion (62.4% vs 30.8%, χ^2=20.921, p<0.001), and stage T3-T4 (17.2% vs 4.3%, χ^2=9.626, p=0.002) proportions than those without LNM. Age, gender, thyroid function, and preoperative CTCs level between patients without and with LNM had no statistically significant difference (Table 3).

Table 3 Comparison of Clinicopathological Features Between PTC with and without LNM in Patients with Hashimoto's Thyroiditis

Clinicopathological Features	Non-LNM (n=117)	LNM (n=93)	*p* (χ^2)
Age (Years)			
<55, n (%)	97(82.9%)	80(86.0%)	0.572
≥55, n (%)	20(17.1%)	13(14.0%)	(χ^2=0.380)
Gender			
Male, n (%)	11(9.4%)	12(12.9%)	0.506
Female, n (%)	106(90.6%)	81(87.1%)	(χ^2=0.651)
Thyroid function			
Normal, n (%)	98(83.8%)	85(91.4%)	0.145
Abnormal, n (%)	19(16.2%)	8(8.6%)	(χ^2=2.697)
Multifocality			
No, n (%)	92(78.6%)	50(53.8%)	<0.001
Yes, n (%)	25(21.4%)	43(46.2%)	(χ^2=14.636)

(*Continued*)

Table 3 (Continued).

Clinicopathological Features	Non-LNM (n=117)	LNM (n=93)	*p* (χ^2)
Maximum lesion diameter			
≤1cm, n (%)	97(82.9%)	42(45.2%)	<0.001
>1cm, n (%)	20(17.1%)	51(54.8%)	(χ^2=32.986)
Capsular invasion			
No, n (%)	81(69.2%)	35(37.6%)	<0.001
Yes, n (%)	36(30.8%)	58(62.4%)	(χ^2=20.921)
T stage			
T1-T2, n (%)	112(95.7%)	77(82.8%)	0.002
T3-T4, n (%)	5(4.3%)	16(17.2%)	(χ^2=9.626)
Preoperative CTCs (FU/3mL)			
Negative (<8.7)	37(31.6%)	39(41.9%)	0.148
Positive (≥8.7)	80(68.4%)	54(58.1%)	(χ^2=2.386)

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

Logistic Regression Analysis of Risk Factors of LNM in PTC Coexistent and Non-Coexistent with Hashimoto's Thyroiditis Patients, Respectively

In PTC patients, multifocality (odds ratio (OR): 2.876, 95% confidence interval (CI): 2.072–3.993, $p<0.001$), maximum lesion diameter >1cm (OR: 5.379, 95% CI: 3.823–7.568, $p<0.001$), capsular invasion (OR: 2.787, 95% CI: 2.075–3.745, $p<0.001$), and stage T3-T4 (OR: 4.742, 95% CI: 2.574–8.738, $p<0.001$) were associated with LNM in univariate analysis. In multivariate analysis, multifocality (OR: 2.324, 95% CI: 1.619–3.335, $p<0.001$), tumor size >1cm (OR: 4.046, 95% CI: 2.786–5.875, $p<0.001$), capsular invasion (OR: 1.735, 95% CI: 1.237–2.435, $p=0.001$) were associated with LNM in PTC patients (Table 4).

In PTC patients with Hashimoto's thyroiditis, multifocality (OR: 3.165, 95% CI: 1.735–5.774, $p<0.001$), maximum lesion diameter >1cm (OR: 5.889, 95% CI: 3.133–11.071, $p<0.001$), capsular invasion (OR: 3.729, 95% CI: 2.099–6.623, $p<0.001$), and stage T3-T4 (OR: 4.655, 95% CI: 1.637–13.238, $p=0.004$) were associated with LNM in univariate analysis. In multivariate analysis, multifocality (OR: 2.127, 95% CI: 1.085–4.168, $p=0.028$), tumor size >1cm (OR: 3.858, 95% CI: 1.903–7.823, $p<0.001$), capsular invasion (OR: 2.007, 95% CI: 1.034–3.895, $p=0.040$) were associated with LNM in PTC patients with Hashimoto's thyroiditis (Table 5).

In PTC patients without Hashimoto's thyroiditis, multifocality (OR: 2.805, 95% CI: 1.893–4.158, $p<0.001$), maximum lesion diameter >1cm (OR: 5.262, 95% CI: 3.501–7.910, $p<0.001$), capsular invasion (OR: 2.514, 95% CI:

Table 4 Logistic Regression Analysis of Risk Factors of LNM in PTC Patients

Variables	Univariate		Multivariate	
	OR (95% CI)	*p* values	OR (95% CI)	*p* values
Age (<55/≥55, years old)	1.185 (0.811–1.731)	0.380	1.320 (0.861–2.024)	0.203
Gender (female/male)	0.625 (0.437–0.894)	0.010	0.675 (0.451–1.011)	0.057
Thyroid function (abnormal/normal)	0.501 (0.310–0.810)	0.005	0.553 (0.323–0.947)	0.031
Hashimoto's thyroiditis (no/yes)	1.093 (0.795–1.505)	0.583	1.243 (0.862–1.793)	0.244
Multifocality (yes/no)	2.876 (2.072–3.993)	<0.001	2.324 (1.619–3.335)	<0.001
Maximum lesion diameter (>1cm/≤1cm)	5.379 (3.823–7.568)	<0.001	4.046 (2.786–5.875)	<0.001
Capsular invasion (yes/no)	2.787 (2.075–3.745)	<0.001	1.735 (1.237–2.435)	0.001
T stage (T3-T4/T1-T2)	4.742 (2.574–8.738)	<0.001	1.637 (0.814–3.290)	0.167
Preoperative CTCs (≥8.7/<8.7, FU/3mL)	1.210 (0.905–1.617)	0.198	1.212 (0.875–1.680)	0.247

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

Table 5 Logistic Regression Analysis of Risk Factors of LNM in PTC with and without Hashimoto's Thyroiditis

Variables	PTC with Hashimoto's Thyroiditis				PTC Without Hashimoto's Thyroiditis			
	Univariate		Multivariate		Univariate		Multivariate	
	OR (95% CI)	*p* values	OR (95% CI)	*p* values	OR (95% CI)	*p* values	OR (95% CI)	*p* values
Age (<55/≥55, years old)	1.269 (0.594–2.709)	0.538	1.095 (0.454–2.640)	0.839	1.162 (0.750–1.801)	0.500	1.348 (0.821–2.213)	0.238
Gender (female/male)	0.700 (0.294–1.668)	0.421	0.896 (0.322–2.495)	0.834	0.614 (0.413–0.913)	0.016	0.648 (0.415–1.012)	0.056
Thyroid function (abnormal/normal)	0.485 (0.202–1.165)	0.106	0.448 (0.161–1.243)	0.123	0.511 (0.288–0.906)	0.022	0.540 (0.284–1.027)	0.060
Multifocality (yes/no)	3.165 (1.735–5.774)	<0.001	2.127 (1.085–4.168)	0.028	2.805 (1.893–4.158)	<0.001	2.461 (1.595–3.797)	<0.001
Maximum lesion diameter (>1cm/≤1cm)	5.889 (3.133–11.071)	<0.001	3.858 (1.903–7.823)	<0.001	5.262 (3.501–7.910)	<0.001	4.108 (2.629–6.417)	<0.001
Capsular invasion (yes/no)	3.729 (2.099–6.623)	<0.001	2.007 (1.034–3.895)	0.040	2.514 (1.780–3.550)	<0.001	1.680 (1.128–2.500)	0.011
T stage (T3-T4/T1-T2)	4.655 (1.637–13.238)	0.004	1.422 (0.433–4.671)	0.561	4.852 (2.280–10.325)	<0.001	1.752 (0.739–4.154)	0.203
Preoperative CTCs (≥8.7/<8.7, FU/3mL)	0.640 (0.363–1.129)	0.123	0.564 (0.292–1.090)	0.089	1.530 (1.089–2.149)	0.014	1.560 (1.065–2.285)	0.022

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

1.780–3.550, $p<0.001$), T3-T4 stage (OR: 4.852, 95% CI: 2.280–10.325, $p<0.001$), and positive preoperative CTCs levels (OR: 1.530, 95% CI: 1.089–2.149, $p=0.014$) were associated with LNM in univariate analysis. In multivariate analysis, multifocality (OR: 2.461, 95% CI: 1.595–3.797, $p<0.001$), tumor size >1cm (OR: 4.108, 95% CI: 2.629–6.417, $p<0.001$), capsular invasion (OR: 1.680, 95% CI: 1.128–2.500, $p=0.011$), and positive preoperative CTCs levels (OR: 1.560, 95% CI: 1.065–2.285, $p=0.022$) were associated with LNM (Table 5).

Discussion

At present, the relationship between Hashimoto's thyroiditis and the clinicopathological features of PTC is still controversial, and there are many inconsistent data, which need to be further explored and confirmed. In order to more accurately assess the risk of LNM in the clinic, the corresponding risk factors for PTC coexistent and non-coexistent with Hashimoto's thyroiditis should be identified separately.[28] In this study, multifocality, maximum lesion diameter >1cm, and capsular invasion are risk factors of LNM in PTC coexistent and non-coexistent with Hashimoto's thyroiditis. Positive preoperative CTCs level is associated with LNM in PTC without Hashimoto's thyroiditis, but not in PTC with Hashimoto's thyroiditis.

In present study, there was no statistically significant difference in age, thyroid function, multifocality, tumor size, capsular invasion, T stage, LNM, and preoperative CTCs levels between patients with and without Hashimoto's thyroiditis. Studies have found that PTC patients with Hashimoto's thyroiditis have a lower risk of developing LNM than PTC patients without Hashimoto's thyroiditis.[29–33] PTC patients with Hashimoto's thyroiditis have fewer LNM, and Hashimoto's thyroiditis is thought to have a protective effect on the LNM of PTC.[30,34] Conversely, studies revealed that PTC coexistent with Hashimoto's thyroiditis have an increased risk of developing LNM.[35–37] This study found that there was no relationship between Hashimoto's thyroiditis and LNM in patients with PTC. At present, the relationship between Hashimoto's thyroiditis and LNM in PTC is still controversial, and there are more inconsistent data, which needs to be further explored and confirmed.

Some studies suggested that young, multifocality, larger tumor size, and capsular invasion were risk factors of LNM in PTC.[38,39] For PTC with Hashimoto's thyroiditis, some studies have been reported on the risk factors of LNM. Lou et al found that tumor diameter ≥ 1 cm, multifocality, capsular invasion were risk factors of LNM in PTC with Hashimoto's thyroiditis.[40] Liu et al showed that tumor diameter > 1cm was a risk factor for central LNM in PTC with Hashimoto's thyroiditis.[28] Konturek et al found that multifocality was risk factor of LNM in PTC with Hashimoto's thyroiditis.[41] Some studies found that young and large tumor size were independent risk factors of central LNM in Hashimoto's thyroiditis combined with PTC.[42,43] Risk factors of LNM in PTC non-coexistent with Hashimoto's thyroiditis have been poorly studied. Liu et al showed that male, young age, tumor diameter > 1cm, and multifocality were risk factors for central LNM in PTC patients without Hashimoto's thyroiditis.[28] More studies are needed to reveal whether gender, age, tumor size, and number of lesions are different in the relationship between LNM in PTC coexistent and non-coexistent with Hashimoto's thyroiditis.

CTCs are tumor cells that shed from tumor lesions and enter the blood circulation.[44,45] Some studies believe that CTCs are valuable markers for assisting the diagnosis and differential diagnosis,[46] monitoring the risk of metastasis,[47–49] and evaluating the prognosis of thyroid cancer patients.[50,51] Some studies revealed that CTCs were associated with LNM in PTC patients.[48,49,52] However, the relationship between CTCs and LNM in PTC with and without Hashimoto's thyroiditis remains unclear. Present study suggests that positive preoperative CTCs level was associated with LNM in PTC without Hashimoto's thyroiditis, but not in patients with Hashimoto's thyroiditis. This result provides clinicians with a convenient and valuable indicator to determine surgical decision making and prognosis for PTC non-coexistent with Hashimoto's thyroiditis patients.

CTCs act as the "seeds" of tumor invasion and metastasis, and positive CTCs typically reflects the ability of tumor cells to leave the primary site and enter the peripheral blood.[53] In thyroid tissues without Hashimoto's thyroiditis, there is less lymphocyte infiltration, and the immune surveillance function of the tumor microenvironment is weaker.[54] CTCs are more likely to survive and spread through the lymph-blood pathway, thereby promoting LNM. In addition, the synchrony between tumor invasiveness and the release of CTCs might also be one of the mechanisms. PTC without Hashimoto's thyroiditis often has higher proliferative activity, and tumor cells are more likely to break through the basement membrane and enter the circulation.[11] As LNM is an early metastasis route, it is highly synchronized with the biological process of CTCs release. Conversely, in PTC patients with Hashimoto's thyroiditis, the CTCs positivity was not significantly associated with LNM. It might be the result of the remodeling of the immune microenvironment related to Hashimoto's thyroiditis. The chronic lymphocyte infiltration in the thyroid gland caused by Hashimoto's thyroiditis may trigger a systemic immune response.[55] Even if tumor cells enter the circulation, they can be quickly identified and eliminated, preventing CTCs from effectively colonizing in the lymph nodes. Furthermore, the fibrosis of thyroid tissue[56] and the remodeling of lymphatic networks[57] caused by Hashimoto's thyroiditis may alter the metastasis preferences of tumor cells, making them more likely to invade local lymph nodes rather than enter the bloodstream. Therefore, the CTCs level cannot reflect the status of LNM.

This study suggested that comprehensive consideration of preoperative CTCs level and clinicopathological features (multifocality, maximum lesion diameter, and capsular invasion) can predict LNM in PTC non-coexistent with Hashimoto's thyroiditis patients. Present study provides valuable reference information for the surgical decision making and prognosis for PTC non-coexistent with Hashimoto's thyroiditis patients. However, it has some shortcomings. First, it is a single-center study, which is a local medical institution with a high level, and the patients treated in this center are relatively complex, so the proportion of LNM in PTC patients with Hashimoto's thyroiditis in different regions and hospitals may be different, which is worth further discussion. Secondly, the follow-up time was insufficient, and the follow-up data were not analyzed, so the relationship between the analysis factors in this study and the survival and recurrence of PTC coexistent and non-coexistent with Hashimoto's thyroiditis patients could not be further analyzed, respectively. Finally, based on clinical characteristics, this study analyzed the risk factors of LNM in PTC coexistent and non-coexistent with Hashimoto's thyroiditis patients. In the next step, we plan to carry out relevant studies from the levels of proteomics, immunoomics and genomics.

Conclusions

Regardless of the presence or absence of Hashimoto's thyroiditis, multifocality, maximum lesion diameter >1cm, and capsular invasion were associated with LNM in PTC patients. Positive preoperative CTCs level is associated with LNM in PTC non-coexistent with Hashimoto's thyroiditis patients, but not in PTC coexistent with Hashimoto's thyroiditis patients. In other words, those with positive preoperative CTC levels, tumor diameter >1cm, multifocality, and capsular invasion have more likelihood to develop LNM in PTC patients without Hashimoto's thyroiditis. In clinical practice, a differentiated and personalized LNM risk assessment plan should be formulated based on whether PTC patients have Hashimoto's thyroiditis. For patients without Hashimoto's thyroiditis, with positive preoperative CTC levels, tumor diameter >1cm, multifocality, and capsular invasion, enhanced lymph node monitoring is required. Of course, the conclusions of this study require further researches in the future to verify them, in order to provide more sufficient evidence support for the precise diagnosis and treatment of PTC.

Data Sharing Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Ethics Approval and Consent to Participate

All participants were informed of the research procedures and objectives, and this study obtained the informed consent of all participants. The study was approved by the Ethics Committee of Medicine, Meizhou People's Hospital.

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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 declare that they have no competing interests.

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