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The Effects of Hashimoto Thyroiditis on Lymph Node Metastases in Unifocal and Multifocal Papillary Thyroid Carcinoma

A Retrospective Chinese Cohort Study

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Abstract: The purpose of this study was to investigate the risk factors for central and lateral neck lymph node metastases in papillary thyroid carcinoma (PTC) and multifocal papillary thyroid carcinoma (MPTC), particularly when associated with Hashimoto thyroiditis (HT).

A retrospective analysis of 763 consecutive patients who underwent total thyroidectomy with bilateral central neck dissection in the First Affiliated Hospital, College of Medicine, Zhejiang University between October 2011 and October 2014 was conducted. All patients had formal histological diagnoses of HT. Multivariable logistic regression analysis was performed to identify risk factors of neck lymph node metastases.

Our study identified 277 PTC patients with HT and showed comparatively low rates of central lymph node metastases (CLNM) compared with the PTC patients without HT (37.2% versus 54.7%, $P < 0.001$). There were no statistically significant differences in lateral lymph node metastases (LLNM) ($P = 0.656$). Neck lymph node metastases were histologically proven in 127 (45.8%) patients with PTC with HT, including 103 CLNM and 24 LLNM. There were no significant differences in LLNM between the MPTC-associated HT and classic MPTC cases; however, a significantly reduced risk of CLNM was observed in the MPTC-associated HT compared with the MPTC cases (35.7% versus 72.4%, respectively, $P < 0.001$). In the multivariate analysis, HT was identified as an independent alleviating factor for CLNM in all PTC patients (odds ratio, 0.369; 95% confidence interval (CI), 0.261 to 0.521; $P < 0.001$) and in MPTC patients (odds ratio, 0.227; 95% CI, 0.126−0.406; $P < 0.001$). A cut-off of thyroid peroxidase antibody >140 IU/mL was established as the most sensitive and specific level for the prediction of MPTC based on receiver operating characteristic curve analyses. Thyroid peroxidase antibody, age, tumor size, and multifocality exhibited the ability to predict CLNM in PTC with HT patients with an area under the curve of 81.1% based on a multivariate model.

Hashimoto thyroiditis was associated with increased prevalences of multifocality and capsular invasion. In contrast, HT was associated with a reduced risk of CLNM in PTC and MPTC patients, which indicated a potential protective effect. We found that the prognostic prediction model was applicable for predicting multifocality and CLNM in PTC patients with HT.

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Abbreviations: CLNM = central lymph node metastases, HT = Hashimoto thyroiditis, LLNM = lateral lymph node metastases, MPTC = multifocal papillary thyroid carcinoma, NLNM = neck lymph node metastases, PTC = papillary thyroid cancer, TpoAb = thyroid peroxidase antibody.

INTRODUCTION

The incidence of thyroid carcinoma has rapidly increased in recent years, and this condition affects approximately 5 per 100,000 to 15 per 100,000[1] persons. Approximately 70% to 80% of thyroid cancers are papillary thyroid carcinomas (PTCs),[2] which exhibited a relatively benign clinical course. Hashimoto thyroiditis (HT) is the most common form of autoimmune thyroid disease, and the incidence of this disease is approximately 2% of the general population.[3] The relationship between PTC and HT has been controversial. Some investigations have reported HT is a risk factor for PTC, whereas other studies have not observed a positive correlation.[4] The frequency of the association between PTC and HT ranges from 9% to 58% in a series of studies.[5]

Recently, studies have also focused on the influence of HT on the prognoses of PTC patients associated with HT. Some investigators have reported that PTC patients with lymphocytic thyroiditis tend to exhibit a lower frequency of lymph node metastases, less advanced disease, and better prognoses. In contrast, other studies have demonstrated that PTC coexisting with HT is more likely to be bilateral and multifocal.[6,7] Meta-analyses have indicated that HT is present in 26% of multifocal patients compared with 21% of unifocal patients.[6] Interestingly, some studies have revealed that multifocal cases are associated with an increased incidence of central lymph node metastases (CLNM)[8]; however, other studies have found no difference between unifocal and multifocal PTC.[9] Overall, the associations of lymph node metastasis and multifocal papillary thyroid carcinoma (MPTC) with HT are not fully understood.

Although some studies have investigated the clinicopathologic factors of PTC with HT, the prognostic significance of HT in MPTC remains unclear. It is uncertain whether coexisting with HT in PTC and MPTC patients represents a good prognosis or is simply the concurrence of both diseases. It is therefore reasonable to evaluate the influence of HT on lymph node

metastases in PTC and MPTC patients. Notably, most previous studies evaluated PTC with HT. We hypothesize that the presence of HT may be associated with less risk of neck lymph node metastases (NLNM) and a better prognosis. The aim of this study was to evaluate the clinicopathologic features of MPTC with and without associated HT. Additionally, we sought to investigate the risk factors associated with NLNM in MPTC that are concomitant with HT.

MATERIALS AND METHODS

General Information

This study was approved by ethical committees of the First Affiliated Hospital. The informed consent requirement was obtained from each patient. A retrospective review of the Thyroid Disease Diagnosis and Treatment Center database of the First Affiliated Hospital of the College of Medicine of Zhejiang University was performed. The data from the 3-year period between October 2011 and October 2014 were analyzed. All 763 PTC patients underwent total thyroidectomy with bilateral central neck dissection. The male-to-female ratio of the patients was 185:578, and the mean age was 43.98 ± 11.96 years (15–79 years). The patients comprised 277 subjects with histologically proven HT (36.3%) and 486 without HT (63.7%; Table 1). Of the 234 MPTC patients, 129 were observed concomitant with HT (55.1%) and 105 patients without HT (44.9%; Figure 1).

The clinical assessments performed for all patients included assays of thyroid hormone, checks of the serum thyrotropin and thyroid peroxidase antibody (TpoAb) levels, ultrasonic examination of the thyroid and computed tomography examinations of the neck, which were performed preoperatively. Ultrasound-guided fine-needle aspiration (FNA) biopsies were performed in 547 patients. Thyroidectomies were performed in the patients with high levels of suspicion of malignancy

based on prior thyroid FNA and ultrasound examinations. The surgical procedures for the thyroidectomies with bilateral central neck dissection were selected based on the following factors: the presence of suspected malignancy based on thyroid nodules larger than 1 cm with or without contralateral thyroid nodules, suspected malignancy based on the presence of thyroid nodules less than 1 cm with contralateral thyroid nodules larger than 0.5 cm, and multifocal PTC or bilateral PTC. Patients with Graves' disease were excluded. Lateral lymph node dissections were performed in 66 patients who underwent preoperative ultrasonography, computed tomography, or FNA of the lateral lymph nodes due to potential metastasis.

Receiver operating characteristic curves were used to examine the abilities to predict MPTC and CLNM using a multivariate model. A binary logistic regression was performed to identify independent prognostic predictors of CLNM. Finally, we identified four variables, that is, TpoAb, age, tumor size at the time of diagnosis and multifocality. Then a logistic regression analysis of the multivariate model using 4 variables was performed to calculate the prediction probability. Receiver operating characteristic curves were drawn based on data from a classification table using prediction probability ranged from 0 to 1. The predictive value of the established model was assessed by calculating the area under the curve (AUC).

Statistical Analysis

Quantitative data are displayed as the mean $\pm$ the SD. Statistical analyses were performed using the χ^2 test, Fisher exact test, and the t test, as appropriate. Differences with P values <0.05 were defined as statistically significant. The statistical analyses were performed with the SPSS 22.0 program (SPSS, Chicago, IL) for Windows. The sample size was statistically determined using PASS 11.0 (NCSS, LLC).

RESULTS

Comparisons of the Clinicopathologic Features of the Papillary Thyroid Carcinomas Patients With and Without Hashimoto Thyroiditis

Among the 763 patients in this study, HT was present in 277 patients (36.3%) and absent in 486 (63.7%) patients. Central lymph node metastases were histologically proven in 389 patients (48.4%) and lateral lymph node metastases (LLNM) were in 53 patients (6.9%; Table 1). The male-to-female ratios of the patients with and without HT were 1:4.04 and 1:2.74, respectively ($P = 0.033$). Compared with the PTC patients without HT, the PTC patients with HT tended to exhibit multifocality (46.6% versus 21.6%, $P < 0.001$) and greater capsular invasion (43.3% versus. 29.2%, $P < 0.001$). However, there were no statistically significant differences in age (<45 versus ≥ 45 years, $P = 0.333$), tumor size (≤ 1 versus > 1 cm, $P = 0.238$), or serum thyrotropin levels ($P = 0.068$). Additionally, the numbers of CLNM and LLNM were evaluated. Approximately 37.2% (103/277) of the PTC patients with HT exhibited CLNM, and 54.7% (266/486) of the PTC patients without HT exhibited CLNM ($P < 0.001$). There were no statistically significant differences in LLNM ($P = 0.656$), the numbers of metastatic lateral lymph nodes ($P = 0.455$) or laterally removed lymph nodes ($P = 0.059$; Table 2).

Hashimoto Thyroiditis, Multifocal Carcinoma, and Lymph Node Metastases

Compared to the MPTC with HT (129 patients), the unifocal PTC with HT (148 patients) were significantly

TABLE 1. Clinicopathologic Characteristics of the Study Population* (n = 763)

Characteristics	All Patients (n = 763)
Age at diagnosis, y (range)	43.98 ± 11.96 (15–79)
Median age, years	44
$\geq$45 y, n (%)	362 (47.4%)
$<$45 y, n (%)	401 (52.6%)
Sex ratio (M/F)	185/578
Multifocality, n (%)	234 (30.7%)
PTC with HT, n (%)	277 (36.3%)
Capsular invasion, n (%)	262 (34.3%)
Tumor size, cm (range)	1.07 ± 0.75 (0.05–5.50)
CLNM, n (%)	369 (48.4%)
Number of removed CLNs, (range)	5.43 ± 5.03 (0–25)
Number of metastatic CLNs, (range)	1.53 ± 2.44 (0–16)
LLNM†, n (%)	53 (6.9%)
Number of removed LLNs, (range)	16.58 ± 9.79 (1–58)
Number of metastatic LLNs, (range)	4.73 ± 5.37 (0–25)

CLNM = central lymph node metastases, CLNs = central lymph nodes, F = female, HT = Hashimoto thyroiditis, LLNM = lateral lymph node metastases, LLNs = lateral lymph nodes, M = male, PTC = papillary thyroid cancer.
* Values are mean $\pm$ standard deviation, frequency (percentage).
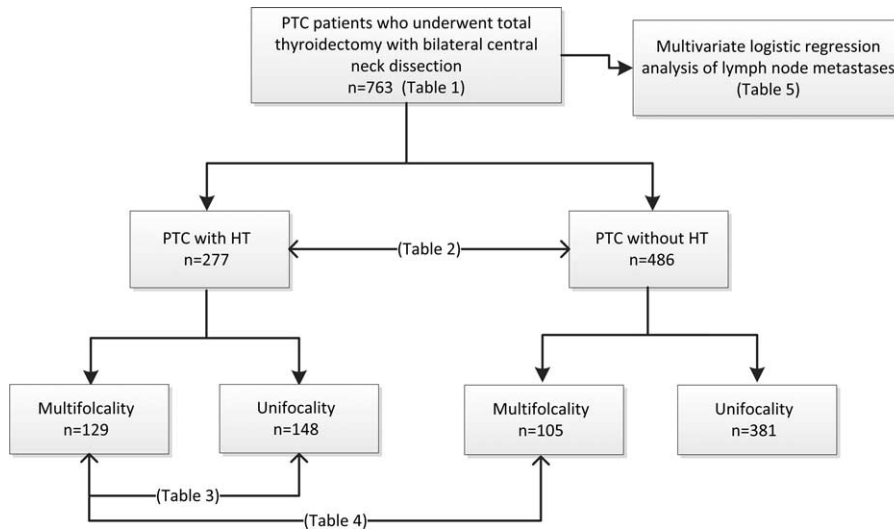† Sixty six patients received lateral neck dissection and LLNM were histological proven in 53 (80.3%) patients.

FIGURE 1. Flow diagram of the study design. Among the 763 papillary thyroid carcinoma patients who underwent total thyroidectomy with bilateral central neck dissection. Hashimoto thyroiditis was present in 277 patients and absent in 486 patients.

associated with the number of metastatic central lymph nodes ($P = 0.003$). However, there was no difference in the CLNM and LLNM ($P = 0.624$ and $P = 0.151$, respectively) (Table 3). Multifocal papillary thyroid carcinomas without HT were observed in 105 patients. In contrast, metastasis to the central compartment was noted in 46 (35.7%) MPTC patients with HT and 76 (72.4%) MPTC patients without HT ($P < 0.001$). No significant differences were observed in LLNM ($P = 0.350$). The 9 patients with confirmed central compartment metastases were more likely to have LLNM (100%) in MPTCs with HT than the 7 patients without HT (77.8%; Table 4).

Risk Factors for Lymph Node Metastases in the Papillary Thyroid Carcinomass and Multifocal Papillary Thyroid Carcinomas

A preoperative multivariate logistic regression analysis that included sex (male/female), age ($\geq 45/<45$ years), tumor size (>1 cm/≤ 1 cm), capsular invasion (present/absent), HT presence (present/absent) and multifocality (present/absent) was used to assess whether these factors were associated with NLNM in PTCs. We found that an age greater than or equal to 45 years (OR = 2.050; 95% CI, 1.504–2.793, $P < 0.001$), tumor size >1 cm (OR = 2.708; 95% CI, 1.831–4.006, $P < 0.001$), and

TABLE 2. Results of the Correlation Between Hashimoto Thyroiditis and Clinicopathological Variables[*]

	HT (n = 277)	Non-HT (n = 486)		*P* Value
Sex ratio (M/F)	55:222	130:356	4.565	0.033
Age at diagnosis, n (%)				
≥ 45 y	125 (45.1%)	237 (48.8%)	0.937	0.333
<45 y	152 (54.9%)	249 (51.2%)		
Tumor size, n (%)				
≤ 1 cm	170 (61.4%)	319 (65.6%)	1.395	0.238
>1 cm	107 (38.6%)	167 (34.4%)		
Multifocality, n (%)	129 (46.6%)	105 (21.6%)	51.719	<0.001
Capsular invasion, n (%)	120 (43.3%)	142 (29.2%)	15.57	<0.001
TSH level, μIU/mL	2.95 ± 8.54	2.20 ± 3.35	t = 1.423	0.068
Number of removed CLNs	5.81 ± 5.16	5.22 ± 4.94	t = 1.562	0.189
Number of metastatic CLNs	1.87 ± 3.14	1.34 ± 1.91	t = 2.92	<0.001
CLNM, n (%)	103 (37.2%)	266 (54.7%)	21.76	<0.001
Number of removed LLNs	8.00 ± 5.77	4.14 ± 4.45	t = 2.27	0.059
Number of metastatic LLNs	19.29 ± 8.69	13.79 ± 7.23	t = 2.516	0.455
LLNM, n (%)	24/29 (82.8%)	29/37 (78.4%)	0.199	0.656

CLNM = central lymph node metastases, CLNs = central lymph nodes, HT = Hashimoto thyroiditis, LLNM = lateral lymph node metastases, LLNs = lateral lymph nodes, M = male; F = female, TSH = thyroid stimulating hormone.
[*] Values are mean ± standard deviation, frequency (percentage).

TABLE 3. Comparison of Neck Lymph Node Metastases of Papillary Thyroid Cancer With Hashimoto Thyroiditis According to the Presence of Multifocality[*]

PTC With HT	Multifocality (n = 129)	Unifocality (n = 148)		*P* Value
Number of removed CLNs	5.85 ± 5.14	5.78 ± 5.20	t = 0.109	0.653
Number of metastatic CLNs	1.53 ± 2.85	2.17 ± 3.35	t = −1.683	0.003
CLNM, n (%)	46 (35.7%)	57 (38.5%)	0.24	0.624
Number of LLN removed	22.1 ± 13.67	17.1 ± 8.1	t = 1.211	0.159
Number of LLN metastases	8.14 ± 6.47	5.2 ± 5.5	t = 1.323	0.371
LLNM, n (%)	13/14 (92.9%)	11/15 (73.3%)	2.06	0.151

CLN = central lymph node, CLNM = central lymph node metastases, HT = Hashimoto thyroiditis, LLN = lateral lymph node, LLNM = lateral lymph node metastases, NLNM = neck lymph node metastases, PTC = papillary thyroid cancer.
[*] Values are mean ± standard deviation, frequency (percentage).

the presence of HT (OR = 0.369; 95% CI, 0.261–0.521, $P < 0.001$) were noted to be significantly associated with CLNM in PTCs. However, no variables were found to be significantly associated with LLNM (Table 5). We next investigated the risk factors associated with CLNM in MPTCs. Hashimoto thyroiditis was a significant independent alleviating factor for CLNM in MPTCs, with an odds ratio of 0.227 (95% CI, 0.126–0.406, $P < 0.001$; Table 6).

Receiver Operating Characteristic Curve Analyses for Multifocal Papillary Thyroid Carcinoma and Central Lymph Node Metastases

Receiver operating characteristic curves were used to predict multifocality (Figure 2A and B). The AUCs and *p* values that were calculated for the PTC and PTC with HT patients for multifocality were 54.5% ($P < 0.05$) and 84.3% ($P < 0.0001$), respectively, which indicated that the TpoAb value could accurately predict multifocality in patients with PTC with HT. Thyroid peroxidase antibody, age, tumor size and the presence of multifocality were included in the multivariate logistic regression analysis (Table 7). We created the multivariate model to calculate the probability for predicting CLNM. Receiver operating characteristic curve analysis was also performed to predict CLNM in both the PTC and PTC with HT patient (AUCs: 73.4% and 81.1%, respectively, $P < 0.0001$; Figure 2C and D).

DISCUSSION

Hashimoto thyroiditis, also known as chronic lymphocytic thyroiditis and was first described by Hakaru Hashimoto in 1912. Hashimoto thyroiditis is the most common form of autoimmune thyroid disease.[10] The incidence of HT is approximately 0.3 to 1.5 cases per 1000 persons every year.[3] The main pathological abnormalities include lymphocytic infiltration and oxyphilic changes that can lead to fibrous variants and parenchymal atrophy.[11] Hashimoto thyroiditis is widely considered to be associated with thyroid dysfunction and the development of thyroid nodules.[12] Papillary thyroid carcinoma is another of the most common endocrine malignancies, and the incidence of this condition has rapidly increased in recent years.[13] The relationship between PTC and HT was first described in 1955 by Dailey.[14] Since that time, numerous studies have focused on this link, but it still remains a controversial issue. In systematic literature reviews, the average prevalences of PTC in patients with HT have been found to be 1.2% in FNAB studies and 27.56% in thyroidectomy studies.[15] In contrast, one meta-analysis demonstrated that the coexistence of HT was significantly associated with PTCs compared with benign lesions and other thyroid carcinomas. This finding implies that HT may indeed be a risk factor for the development of PTC.[6] Although some clinical studies have reported a positive correlation between HT and PTC, the immunological mechanisms of this association remain unknown.

Tumor multifocality is typically present in PTC patients, and the prevalence of multifocality ranges from 18% to 87%.[16,17] Although high-resolution ultrasonography and FNAB have been used to diagnose MPTC, some small tumor foci are frequently found postthyroidectomy.[17] The association between lymph node metastasis and MPTC remains controversial. Some studies have indicated that multifocality results in an increased

TABLE 4. Comparison of Neck Lymph Node Metastases of Multifocal Papillary Thyroid Carcinoma According to the Presence of Hashimoto Thyroiditis[*]

MPTC	HT (n = 129)	Non-HT (n = 105)		*P* Value
Number of CLN removed	5.85 ± 5.14	6.59 ± 5.53	t = −1.067	0.809
Number of CLN metastases	1.53 ± 2.85	2.01 ± 2.06	t = −1.429	0.014
CLNM, n (%)	46 (35.7%)	76 (72.4%)	31.28	<0.001
Number of removed LLNs	22.1 ± 13.67	12.5 ± 9.28	t = 1.915	0.422
Number of metastatic LLNs	8.14 ± 6.47	4.3 ± 7.45	t = 1.347	0.655
LLNM, n (%)	13/14 (92.9%)	8/10 (80.0%)	0.872	0.350

CLNM = central lymph node metastases, CLNs = central lymph nodes, HT = Hashimoto thyroiditis, LLNM = lateral lymph node metastases, LLNs = lateral lymph nodes, MPTC = multifocal papillary thyroid carcinoma, NLNM = neck lymph node metastases.
[*] Values are mean ± standard deviation, frequency (percentage).

TABLE 5. Multivariate Logistic Regression Analysis of Variables Associated With Central and Lateral Lymph Node Metastases in All Patients

Variables	OR	95% CI	P Value
CLNM			
Sex (male/female)	1.413	0.987–2.022	0.059
Age (≥45/< 45 y)	2.050	1.504–2.793	<0.001
Tumor size (>1 cm/≤1 cm)	2.708	1.831–4.006	<0.001
Capsular invasion (present/absent)	1.360	0.913–2.027	0.130
HT (present/absent)	0.369	0.261–0.521	<0.001
Multifocality (present/absent)	1.020	0.978–1.065	0.340
LLNM			
Sex (male/female)	4.144	0.439–39.089	0.214
Age (≥45/<45 y)	3.209	0.819–12.576	0.094
Tumor size (>1 cm/≤1 cm)	0.104	0.010–1.059	0.056
Capsular invasion (present/absent)	7.539	0.913–62.269	0.061
HT (present/absent)	0.679	0.148–3.124	0.619
Multifocality (present/absent)	2.432	0.469–12.608	0.290

CI = confidence interval, CLNM = central lymph node metastases, HT = Hashimoto thyroiditis, LLNM = lateral lymph node metastases, OR = odds ratio.

incidence of CLNM[8] but other studies have found no difference between unifocal and multifocal PTC.[9]

In the present study, we found the rate of HT in patients with PTC was 36.3% and that in the patients with MPTC, the rate of HT was 55.1%. Recently, studies of this topic similarly demonstrated that the prevalence of PTC in patients with HT have been found to be 29.4%~58.3% in the same region.[18,19] The rate of HT was higher among the patients with MPTC compared with those with PTC. In contrast, our study revealed that multifocal papillary thyroid cancer is approximately twice as frequent as PTCs in patients with Hashimoto thyroiditis, which suggests that HT may predispose patients to the development of MPTC. Capsular invasion was more frequently noted than CLNM in PTCs with HT. However, the tumor sizes, ages at the time of diagnosis, and the frequencies of lateral lymph node metastasis in PTCs with and without HT were similar. Our study revealed that a TpoAb > 140 IU/mL predicted the occurrence of MPTC; thus, surgeons should give more attention to tumor multifocality when they encounter histologically proven Hashimoto thyroiditis and PTCs during surgery.

TABLE 6. Multivariate Logistic Regression Analysis of Central Lymph Node Metastases in Multifocal Papillary Thyroid Carcinoma Patients

Variables	OR	95% CI	P Value
Sex (male/female)	1.495	0.726–3.081	0.275
Age (≥45/<45 y)	1.608	0.908–2.849	0.103
Tumor size (>1 cm/≤1 cm)	1.797	0.919–3.511	0.087
Capsular invasion (present/absent)	1.526	0.779–2.991	0.218
HT (present/absent)	0.227	0.126–0.406	<0.001

CI = confidence interval, HT = Hashimoto thyroiditis, OR = odds ratio.

Although PTC is generally an indolent disease that has an excellent prognosis,[20] reducing the risk of recurrence and postoperative complications is important. Certain clinicopathological features, such as age at the time of diagnosis, tumor size, extrathyroidal extension, multiple centricity, lymph node metastasis, and distant metastasis, are capable of predicting recurrences in patients treated with surgery.[21–26] There are no recent unambiguous clinical studies that have indicated whether HT predisposes patients to cancer recurrence. Several articles have reported that the presence of HT in PTC is associated with smaller tumor size, less tumor invasion, a lower frequency of lymph node metastasis, less advanced TNM stage, and better prognosis.[7,27–29] In contrast, other studies have reported that PTCs that coexist with HT are more likely to be bilateral and multifocal, resulting in a higher frequency of lymph node metastases.[30–32]

We noticed that the frequency of CLNM in PTC patients with HT was less than that in the patients without HT and that the difference was more significant in MPTC patients. Moreover, there were no statistically significant differences in LLNM. When lymph node metastasis was present in the central compartment of the necks of patients with MPTC, 100% (9/9) of the HT patients exhibited lateral lymph node metastasis involvement, whereas 77.8% (7/9) of the patients without HT exhibited such involvement. In the multivariable analysis, the presence of HT was noted as significantly associated with CLNM in patients with MPTC, which was indicative of a complicated interaction of lymph node metastases in PTC and HT. We used a multivariate model that involved TpoAb, age, tumor size at the time of diagnosis, and multifocality. The sensitivity and specificity of CLNM in the PTC patients (cutoff probability value: 0.513) were 63.5% and 72.8%, respectively, and in the PTC with HT patients (cutoff probability value: 0.478), these values were 64.1% and 84.2%, respectively.

In recent years, the coexistence of thyroid cancer and HT has been of great concern, but the mechanisms related to the relationship between them have remained unclear. So far, the main molecular finding is the mutations of oncogene BRAF (B-type Raf kinase)^{V600E} and the recombination of RET/PTC (Rearranged during transfection).[33] Although RET/PTC-induced signaling of thyroid cells is mediated through the MAPK (Mitogen-activated protein kinase) pathway,[34] it has been recognized that BRAF mutant is another stronger cause of aberrant activation of the pathway.[35] Bozec A et al[36] indicated that HT may be the activator of MAPK signaling pathway in the development of PTC. Many studies have investigated a significant association of BRAF^{V600E} mutation with lymph node metastasis.[37,38] Some studies revealed that CLNM was accompanied by high prevalence of BRAF^{V600E} mutation.[39,40] The relationship of BRAF^{V600E} mutation with HT in PTC patients' lymph node metastases remains unknown. In addition, other studies have reported that CST6 (Cystatin E/M) and CXCL14 (Chemokine (C-X-C motif) ligand 14) genes, which have a strong correlation with BRAF^{V600E} mutation were associated with CLNM in PTC patients.[41] Nonetheless, whether these genes and HT are linked in PTC patients is still unknown.

Whether HT represents a host immune response to PTC or just a chance occurrence remains unclear. Ehlers et al[42] postulated several possible pathomechanisms and reported that thyroid carcinoma develop despite, or due to, immune responses. Hashimoto thyroiditis is a most common autoimmune thyroid disease, and the thyroid-specific immune response is one of the relevant pathological processes. In addition, several studies have demonstrated that cancer
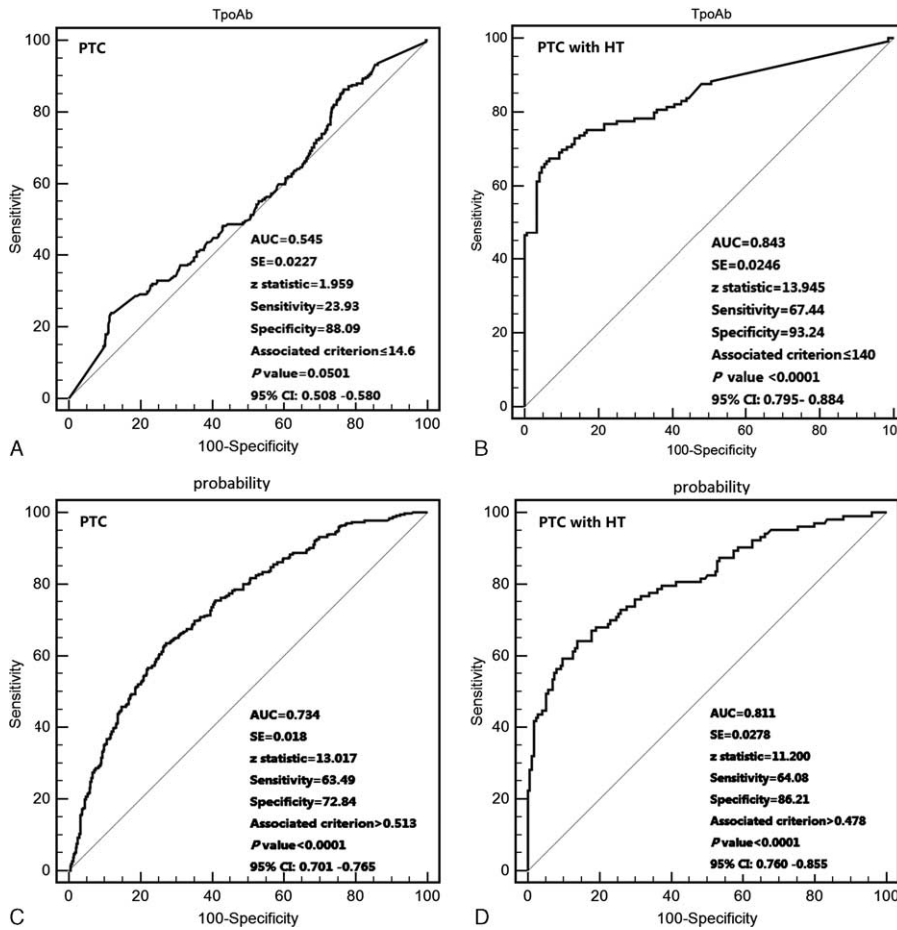
FIGURE 2. Receiver operating characteristic curve analyses of thyroid peroxidase antibody for predicting multifocal papillary thyroid carcinoma (A and B). Receiver operating characteristic curve analyses for prediction of central lymph node metastases using the multivariate model (C and D). This Receiver operating characteristic curve using probability cut offs from 0 to 1 (see methods). (A and C): All papillary thyroid cancer patients (n = 763). (B and D): papillary thyroid cancer patients with HT (n = 277).

immunosurveillance process can eliminate malignant cells. The infiltration of $CD4^+$, $CD8^+$, and Th17 cells is important in the immune-escape mechanisms of PTC and result in a decreased immune response that leads to a favorable prognosis.[43]

Although few published studies have evaluated the association between CLNM of PTC patients with HT, we confirm the findings that HT in patients with PTC was associated with a low

TABLE 7. Multivariate Analyses of Variables for the Prediction of Central Lymph Node Metastases in Papillary Thyroid Carcinoma Patients With Hashimoto Thyroiditis

Variables	OR	95% CI	P Value
TpoAb	0.998	0.997−0.999	<0.001
Age	0.971	0.946−0.996	0.023
Tumor size	3.238	1.989−5.272	<0.001
Multifocality (present/absent)	4.286	1.992−9.222	<0.001

CI = confidence interval, OR = odds ratio, TpoAb = thyroid peroxidase antibody.

probability of CLNM. The strength of our study relates to the analysis of CLNM in MPTC patients, as well as the effects of HT on CLNM in MPTCs. We also indicated that the TpoAb value could predict multifocality in patients with PTC with HT and evaluated the ability of the model for predicting CLNM in PTC with HT patients. Furthermore, this model could be applied in clinical practice. Nonetheless, our study had several limitations. First, our study was a retrospective and from a single center. A multicenter prospective study will be more helpful for finding out intrinsic effects of HT on CLNM. Second, more research on the mechanism of the molecular biology is needed for explanation of the correlations observed in the future. Finally, we indicated that HT was associated with a reduced risk of CLNM in MPTC patients. Hashimoto thyroiditis was reported to be associated with improved prognosis in PTC patients with CLNM.[7] Whether the similar influence in MPTC patients with CLNM remain unknown. Further follow-up study should be explored in future to evaluate the prognosis of HT in MPTC patients.

In conclusion, our results provide the consecutive analysis of the relationship between HT and PTC, demonstrated that HT may influence lymph node metastases in the necks of MPTC patients. Hashimoto thyroiditis was associated with

multifocality and a reduced risk of CLNM, even in MPTC patients, which indicated a potential protective effect.

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