Multifocal Papillary Thyroid Carcinoma，Hashimoto's Thyroiditis and Lymph Node Metastasis：A Retrospective Cohort Study

Denghui Wang
The First Affiliated Hospital of Chongqing Medical University
Jiang Zhu
The First Affiliated Hospital of Chongqing Medical University
Chang Deng
The First Affiliated Hospital of Chongqing Medical University
Zhixin Yang
The First Affiliated Hospital of Chongqing Medical University
Daixing Hu
The First Affiliated Hospital of Chongqing Medical University
Xiujie Shu
The First Affiliated Hospital of Chongqing Medical University
Ping Yu
The First Affiliated Hospital of Chongqing Medical University
Xinliang Su (suxinliang@21cn.com)
The First Affiliated Hospital of Chongqing Medical University https://orcid.org/0000-0001-5792-1407

Research

Keywords: central lymph node metastases(CLNM), lateral lymph node metastases(LLNM)

Posted Date: February 9th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-194311/v1

Multifocal Papillary Thyroid Carcinoma，Hashimoto's Thyroiditis and Lymph Node Metastasis：A Retrospective Cohort Study

Denghui Wang,[1] Jiang Zhu,[1] Chang Deng,[1] Zhixin Yang,[1] Daixing Hu,[1] Xiujie Shu,[1] Ping Yu,[1]

①Department of Endocrine and Breast Surgery, The First Affiliated Hospital of Chongqing Medical University, 1 Youyi Road, Chongqing 400016, People's Republic of China

Correspondence: XinLiang Su

Department of Endocrine and Breast Surgery, The First Affiliated Hospital of Chongqing Medical University, 1 Youyi Road, Chongqing 400016, People's Republic of China

Tel +86 135 0830 9161

Fax +86 23 8901 1463

Email suxinliang@21cn.com

Abstract:

Objective:Few studies have evaluated the influence of HT and Multifocality on central lymph node metastases(CLNM) and lateral lymph node metastases(LLNM) of PTC. The present study focused on risk factors for lymph node metastasis in PTC according to the presence of HT or multifocality. Materials and methods:1413 patients were identified.The relationship between HT or multifocality and lymph node metastasis was analyzed by univariate and multivariate logistic regression, ROC

curves were constructed to show the predictive effect of each variable on the target outcome.

Results: The PTCs with HT were more likely to be multifocal.(40.0% versus 17.5%,P ＜0.001). Compared to MPTC without HT, MPTC with HT showed a lower number of metastatic CLNs and LLNs (P < 0.05). HT was identifified as an independent protective factor for CLNM in all PTC patients (OR, 0.480; 95% CI, 0.359-0.643; P< 0.001) and in MPTC patients (OR, 0.094; 95% CI, 0.044-0.204; P < 0.001), the multicocality was independent risk factors for CLNM(OR, 2.316; 95% CI, 1.667-3.217; P< 0.001) and LLNM(OR, 2.004; 95% CI, 1.469-2.733; P< 0.001).The variables concluded HT or MPTC were screened to predict CLNM in all patients, CLNM in patients with MPTC and LLNM in all patients (AUCs: 0.731, 0.843 and 0.696, respectively, P < 0.0001). The two type of diseases existed concurrently may result in the decrease of CLNM and LLNM, AUCs of ROC to predict CLNM and LLNM are 0.696 and 0.63(P<0.0001).

Conclusions:Our study identified multifocality as an independent risk factor predicting CLNM and LLNM in PTC patients. HT was proven to be a protective factor that reduced the CLNM risk in all patients and in patients with MPTC. The existence of both type of diseases can result in the reduction of CLNM and LLNM.

INTRODUCTION

As the most common endocrine tumor, thyroid carcinoma has rapidly increased in incidence in recent years and was estimated to account for approximately 90.0 per 1000 and 6.8 per 1000 of the thyroid cancer incidence rate and mortality rate in China in 2015[1][2]. Approximately 85% of thyroid cancers are papillary thyroid carcinomas (PTCs) [3] ,which exhibit a relatively benign clinical course.

Hashimoto thyroiditis (HT) is the most common form of autoimmune thyroid disease [4], with an incidence of approximately 3.5-5 cases per 1000 persons per year [5]. HT was first described by Hakaru Hashimoto in 1912 as “lymphomatous struma” [6].

The relationship between HT and PTC has been controversial for a long time in the literature since its initial description by Dailey et al. in 1955 [7]. Some investigations have reported that HT is a risk factor for PTC, whereas other studies have not observed a positive correlation.The frequency of the association between PTC and HT ranges from 0.5% to 30% in a series of studies [8] .

Recently, the prognosis of PTCs with HT has attracted attention.Despite the fact That this link has been the subject of numerous studies, there is no unanimous scientific literature opinion, and the medical debate remains open.Some published studies have reported that PTC with HT has a lower risk of lymph node metastasis and lower capsule invasion, which seems to suggest a favorable prognosis.However, other investigations have yielded conflicting results showing that HT has no significant protective effects,while still other studies have revealed that PTC with HT is more

likely to be multifocal [9] [10] [11].Interestingly, some studies have reported that multifocal tumors are more likely to have lymph node metastasis [12]. Other studies have found no difference between unifocal and multifocal PTC[13].To date, there is no unanimous opinion in the scientific literature, even though this link has been the subject of numerous studies.

Even if PTC has a good prognosis [14], the presence of regional lymph nodemetastasis is still extremely important for the prognosis of this disease. The lymph node status of MPTC with HT is still uncertain. At present, there are few studies on the relationship between MPTC or HT and LNM , The purpose of the present investigation:(1)evaluate the lymph node status of PTC according to the presence of multifocality and HT(2) explore the risk factors for lymph node metastasis of PTC combined with multicocality and HT.

MATERIALS AND METHODS

General information

This study was approved by the ethical committees of the First Affiliated Hospital of Chongqing Medical University. The required informed consent was obtained from each patient.Data from January 2017 to December 2018 were analyzed.All 1413 PTC patients who underwent total thyroidectomy with unilateral central neck dissection were retrospectively collected in this study.Tumor size was defined as the largest diameter measured by preoperative ultrasound. Multifocality

was defined as more than 1 foci of PTC in total (either in the same lobe or different lobes). We reviewed the electronic medical records and surgical pathology reports of each patient to define initial clinicopathological features, including age at diagnosis, tumor size, capsular characteristics, HT, multifocality, central lymph node metastasis (CLNM),lateral lymph node metastasis (LLNM), thyroid stimulating hormone (TSH), antithyroglobulin antibodies(TGAb), and thyroid peroxidase antibodies (TPOAb).

Thyroidectomies were performed in patients with high levels of suspicion of malignancy based on prior thyroid FNA and ultrasound examinations.Extension of the thyroidectomy was decided upon by the endocrinologist and operating surgeon, depending on the extension of lesions, patient approval and intraoperative findings.Patients who underwent total thyroidectomy were required to meet the following criteria: (1)the presence of a suspected malignancy whose diameter was greater than 1 cm; (2)suspected malignancy based on the presence of thyroid nodules less than 1 cm with nodules in the contralateral thyroid, which were defined as being in more than 3 categories by TI-RADS; (3)coexistence with HT; (4)capsule invasion found by preoperative or intraoperative ultrasound (5)intraoperative frozen section examination revealing the metastatic involvement of lymph nodes.

The inclusion criteria were as follows: (1) All patients were treated for the first time, and their postoperative pathology was confirmed to be PTC. (2) The patient's medical records and relevant examination information, such as ultrasound, thyroid function, thyroid auto-antibodies, and postoperative pathological records, were

complete.(3)The surgical method involved total thyroidectomy with unilateral central neck dissection.

Statistical analysis

For continuous data,we use the mean and standard deviation to describe the data statistically.T test and analysis of variance were adopted to hypothesize the data that met a normal distribution and homogeneity test of variance; otherwise, we used the rank-test. We used case numbers and percentages to describe the discrete data statistically and used the chi-square test to conduct a hypothesis test. To study the risk factors related to the tumor lymph node metastasis, we used logistic regression, and then the ROC curve was created to show the predictive effect of each variable on the target outcome. $P<0.05$ was considered statistically significant. All studies used SPSS 22.0 to perform the analyses.

RESULTS

Comparisons of the Clinicopathologic Featuresof Papillary Thyroid Carcinoma Patients with and without Hashimoto Thyroiditis

In the study including 1413 patients,395(28%) patients had HT,while 1018(72%) did not.Central lymph node metastases were pathologically confirmed in 921 patients (48.4%), and lateral lymph node metastases (LLNM) were confirmed in 469 patients (52.4%; Table 1).The male-to-female ratio of patients with HT was 1:5.81, which is higher than that of patients without HT(1:2.46).Compared with PTC without HT, PTC

patients with HT tended to be younger(p<0.001), multifocal (40.0% versus 17.5%, P < 0.001)and have a larger tumor diameter(11.06±7.10versus11.42±6.37, P=0.034); however,there were no statistically significant differences in capsule formation (26.6% versus 28%, P =0.594).The numbers of CLNM and LLNM were additionally assessed. Patients with HT had more removed lymph nodes than patients without HT (15.17±8.12versus10.27±6.6, p<0.001). However, there were no statistically significant differences in CLNM(P=0.154),the number of metastatic CLNs(P=0.884), the number of removed LLNs(P=0.238), and the number of metastatic LLNs(P=0.415).Furthermore, the levels of TSH(3.37±3.17versus2.58±2.56, P<0.001), TGAb(145.48±356.04versus13.22±89.41, P<0.001)and TPOAb(234.05±308.91versus8.21±48.07, P<0.001)in patients with HT were higher than those in patients without HT(Table 2).

TABLE 1. Clinicopathologic Characteristics of the Study Population

Characteristics	ALL patients (n=1413)
Age at diagnosis, y (M±SD, range)	42.44±12.02 (7-85)
Sex ratio (M/F)	352/1061
Tumor size, mm(M±SD, range)	11.16±6.90，1-50，10
Capsular, n (%)	390 (27.6%)
PTC with HT,n (%)	395 (28%)

Multifocality,n (%)	336 (23.8%)
CLNM, n (%)	921 (65.2%)
Number of removed CLNs (M±SD, range)	11.66±7.37 (1-54)
Number of metastatic CLNs (M±SD, range)	2.66±3.53 (0-25)
LLNM, n (%)	469 (52.4%)
Number of removed LLNs (M±SD, range)	21.47±12.34 (1-86)
Number of metastatic LLNs (M±SD, range)	2.20±3.61 (0-32)
TSH(M±SD, range)	2.80±2.77 (0.01-59.86)
TGAb(M±SD, range)	50.19±211.32 (0.1-2523)
TPOAb(M±SD, range)	71.34±196.4 (0-1027)

1 CLNM = central lymph node metastases, CLNs =central lymph nodes, HT = Hashimoto
2 thyroiditis, LLNM =lateral lymph node metastases, LLNs=lateral lymph nodes.
3 Values are expressed as the mean± standard deviation and frequency (percentage).

4 Table 2. Comparison of the Correlation Between Hashimoto Thyroiditis and

5 Clinicopathological Features

		Non-HT (1018)	HT (n=395)	z/c^2	*P*
Age at diagnosis, y, (M±SD)		43.37±12.09	40.06±11.53	4.519	<0.001
Sex ratio	M	294 (28.9)	58 (14.7)	30.662	<0.001
	F	724 (71.1)	337 (85.3)		
Tumor size, (M±SD)		11.06±7.10	11.42±6.37	2.117	0.034
multifocality,n (%)	no	840 (82.5)	237 (60)	79.591	<0.001
	Yes	178 (17.5)	158 (40)		
Capsular,n (%)	No	733 (72)	290 (73.4)	0.285	0.594
	yes	285 (28)	105 (26.6)		
CLNM, n (%)	No	343 (33.7)	149 (37.7)	2.034	0.154
	Yes	675 (66.3)	246 (62.3)		
Number of removed CLNs (M±SD)		10.27±6.6	15.17±8.12	11.016	<0.001
Number of metastatic		2.63±3.47	2.73±3.68	0.147	0.884

CLNs (M±SD)					
LLNM, n (%)	No	301 (48.0)	119(46.7)	0.130	0.718
	Yes	326 (52.0)	136(53.3)		
Number of removed LLNs (M±SD)		21.21±12.13	22.09±12.84	1.180	0.238
Number of metastatic LLNs (M±SD)		2.10±3.52	2.41±3.83	0.816	0.415
TSH ((M±SD)		2.58±2.56	3.37±3.17	5.264	<0.001
TGAb ((M±SD)		13.22±89.41	145.48±356.04	22.593	<0.001
TPOAb ((M±SD)		8.21±48.07	234.05±308.91	21.140	<0.001

CLNM = central lymph node metastases, CLNs =central lymph nodes, HT = Hashimoto thyroiditis, LLNM =lateral lymph node metastases, LLNs=lateral lymph nodes.Values are expressed as the mean± standard deviation and frequency (percentage).

Hashimoto's Thyroiditis, Multifocal Carcinoma, and Lymph Node Metastases

Among the patients with HT**,** no significant differences were observed in CLNM(P=0.330) and LLNM(P=0.142) between the MPTC (n=158) and UPTC (n=237) groups (Table 3). A total of 336 patients with MPTC were included and grouped according tothe presence of HT.Compared to the patients without HT,the patients with HT were inclined to have less CLNM(65.2% versus 93.3%, P < 0.001),

fewer metastatic CLNs(3.01±4.03 versus 5.16±4.36, P < 0.001), a smaller number of metastatic LLNs(2.70±3.95 versus 3.93±4.88, P =0.010) and LLNM(58.6% versus71.3%, P=0.028)(Table 4). When multifocality and HT existed at the same time,the number of metastases of CLNs, the number of metastases of LLNs, and the LLNM was higher than that of UPTC without HT(1.46±2.18 versus2.09±3;0.042.0.31±0.56versus 1.43±2.57,p=0.001; 16 (26.2%)versus 207 (45.0%), p=0.005).(Table 5)

TABLE 3 Comparison of Neck Lymph Node Metastases of Papillary Thyroid Cancer Combined with Hashimoto's Thyroiditis Based on the Presence of Multifocality

PTC with HT	Unifocal (n=237)	Multifocal (n=158)	z/χ^2	*P*
CLNM, n (%)	143 (60.3)	103 (65.2)	0.950	0.330
Number of removed CLNs(M±SD)	14.46±7.86	16.24±8.41	2.055	0.040
Number of metastatic CLNs	2.55±3.43	3.01±4.03	0.997	0.319

(M±SD)				
LLNM, n (%)	71/144 (49.3)	65/111 (58.6)	2.156	0.142
Number of removed LLNs (M±SD)	21.22±12.10	23.23±13.71	1.380	0.168
Number of metastatic LLNs (M±SD)	2.18±3.73	2.70±3.95	1.675	0.094

1 CLNM = central lymph node metastases, CLNs =central lymph nodes, HT = Hashimoto
2 thyroiditis, LLNM =lateral lymph node metastases, LLNs=lateral lymph nodes.
3 Values are expressed as the mean±standard deviation and frequency (percentage).

4 TABLE 4 Comparison of Neck Lymph Node Metastases of Multifocal Papillary

5 Thyroid Carcinoma Based on the Presence of Hashimoto's Thyroiditis

MPTC	Non-HT (n=178)	HT (n=158)	z/χ^2	*P*
CLNM, n (%)	166 (93.3)	103 (65.2)	41.308	<0.001
Number of removed CLNs (M±SD)	13.75±7.3	16.24±8.41	2.588	0.010

Number of metastatic CLNs (M±SD)	5.16±4.36	3.01±4.03	6.056	<0.001
LLNM, n (%)	119/167 (71.3)	65/111 (58.6)	4.805	0.028
Number of removed LLNs (M±SD)	25.16±13.97	23.23±13.71	0.899	0.369
Number of metastatic LLNs (M±SD)	3.93±4.88	2.70±3.95	2.564	0.010

1 CLNM = central lymph node metastases, CLNs =central lymph nodes, HT = Hashimoto
2 thyroiditis, LLNM =lateral lymph node metastases, LLNs=lateral lymph nodes.

3 Values are expressed as the mean±standard deviation and frequency (percentage).

4 TABLE 5 Comparison of Neck Lymph Node Metastases of Papillary Thyroid

5 Carcinoma based on the Presence of Hashimoto's Thyroiditis and Multifocality

MPTC	UPTC without HT (n=840)	MPTC with HT (n=158)	z/χ^2	*P*
CLNM, n (%)	509（60.6）	56（51.9）	3.038	0.081
Number of removed CLNs (M±SD)	9.55±6.18	14.94±7.11	7.716	<0.001

Number of metastatic CLNs (M±SD)	2.09±3	1.46±2.18	2.032	0.042
LLNM, n (%)	207（45.0）	16（26.2）	7.751	0.005
Number of removed LLNs (M±SD)	19.78±11.06	20.13±10.51	0.634	0.526
Number of metastatic LLNs (M±SD)	1.43±2.57	0.31±0.56	3.441	0.001

CLNM = central lymph node metastases, CLNs =central lymph nodes, HT = Hashimoto thyroiditis, LLNM =lateral lymph node metastases, LLNs=lateral lymph nodes

Values are expressed as the mean±standard deviation and frequency (percentage).

4 Multivariate logistic regression analysis of CLNM and LLNM in all patients,patients with HT and patients with MPTC.

Multivariate logistic regression analysis reported that there were independent relationships between CLNM and HT, which were found in the univariate analysis in patients with MPTC. Some clinicopathological factors, such as multifocality, were independently correlated with CLNM and LLNM in all patients, and HT was independently correlated with CLNM.The OR for the associations of CLNM with HT was 0.480 in all patients and 0.094 in patients with MPTC(TABLE 7).The ORs for the associations of CLNM and LLNM with multifocality in all patients were 2.316 and 2.004,respectively(TABLE 6). Receiver operating characteristic curves were used to predict CLNM and LLNM in all patients and CLNM in patients with MPTC (AUCs: 0.731,0.842 and 0.690, respectively, P＜0.0001)(Figure 1,Figure 2 and Figure 3).We considered whether to combine HT and MPTC simultaneously as a new variable,which was a protective factor in CLNM and LLNM（OR=0.502，95%CI=0.321-0.785，P<0.001 and OR=0.459, 95%CI=0.250-0.842，P<0.012）. (TABLE 8).Then receiver operating characteristic curve analysis was also performed to predict CLNM and LLNM .(AUCs:0.696 and 0.630，respectively, P＜0.0001)（Figure 4 and Figure 5）

TABLE 6 Multivariate logistic regression analysis of CLNM and LLNM in all patients

		OR	95% CI	*P*
CLNM	Sex	0.459	0.340-0.619	<0.001
	Age at diagnosis	0.965	0.956-0.975	<0.001
	Tumor size	1.062	1.041-1.084	<0.001
	HT	0.480	0.359-0.643	<0.001
	Multifocality	2.316	1.667-3.217	<0.001
	Number of removed CLNs	1.063	1.043-1.084	<0.001
LLNM	Age at diagnosis	0.985	0.974-0.997	0.016
	Tumor size	1.070	1.047-1.093	<0.001
	Multifocality	2.004	1.469-2.733	<0.001
	Number of removed LLNs	1.031	1.017-1.044	<0.001

TABLE 7 Multivariate logistic regression analysis of CLNM and LLNM in MPTC

		OR	95% CI	*P*
CLNM	Sex	0.292	0.106-0.819	0.019
	Age at diagnosis	0.939	0.913-0.966	<0.001
	HT	0.095	0.044-0.204	<0.001
	Number of removed CLNs	1.096	1.044-1.151	<0.001
LLNM	Tumor size	1.104	1.054-1.156	<0.001
	TSH	0.824	0.705-0.962	0.015
	Number of removed LLNs	1.054	1.020-1.073	<0.001

TABLE 8 Multivariate logistic regression analysis of CLNM and LLNM in PTCs based on the Presence of Hashimoto's Thyroiditis and Multifocality

		OR	95% CI	*P*
CLNM	Sex	0.493	0.353-0.689	<0.001
	Age at diagnosis	0.967	0.955-0.978	<0.001

	Tumor size	1.063	1.038-1.09	<0.001
	Number of removed CLNs	1.064	1.039-1.09	<0.001
	Multifocality with HT	0.502	0.321-0.785	0.003
LLNM	Tumor size	1.055	1.027-1.083	<0.001
	Multifocality with HT	0.459	0.25-0.842	0.012
	Number of removed LLNs	1.017	1.001-1.034	0.043

Figure 1 Receiver operating characteristic curve analyses for predicting CLNM in all patients

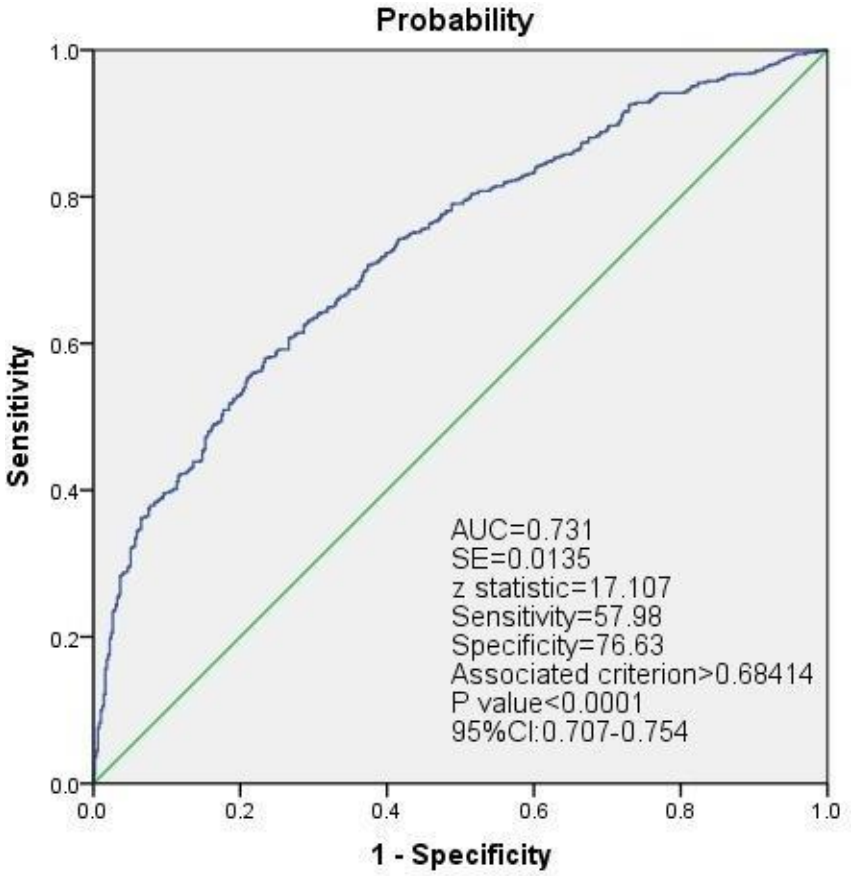
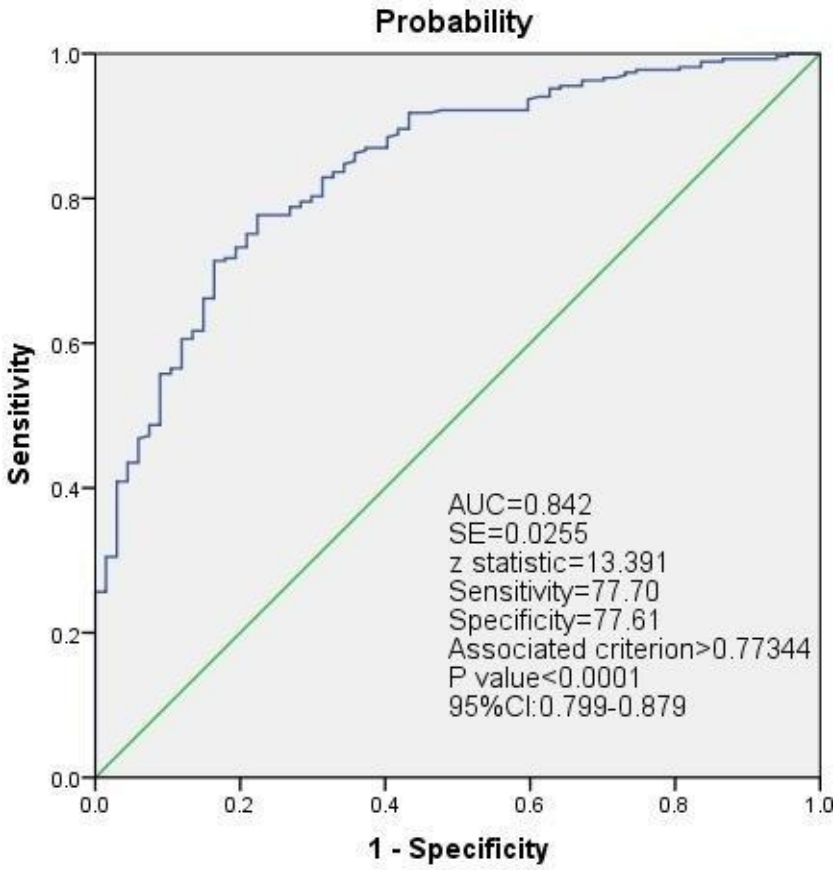


Figure 2 Receiver operating characteristic curve analyses for predicting CLNM in patients with MPTC.



1 **Figure 3** Receiver operating characteristic curve analyses for predicting LLNM

2 in all

patients

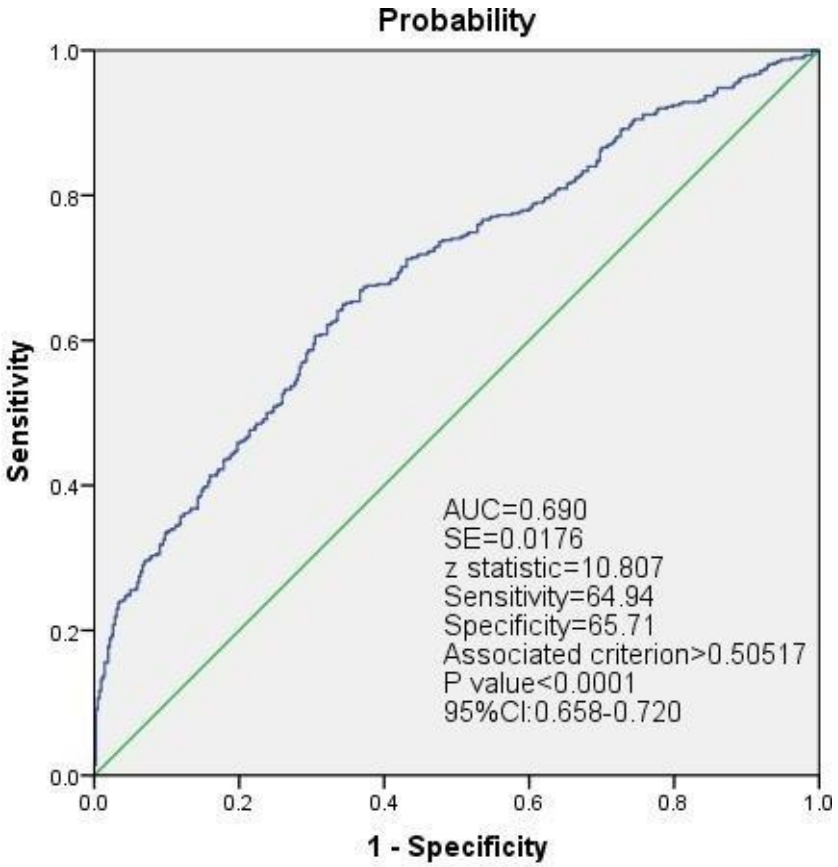


Figure 4 Receiver operating characteristic curve analyses for predicting CLNM in patients with and without MPTC and HT concurrently

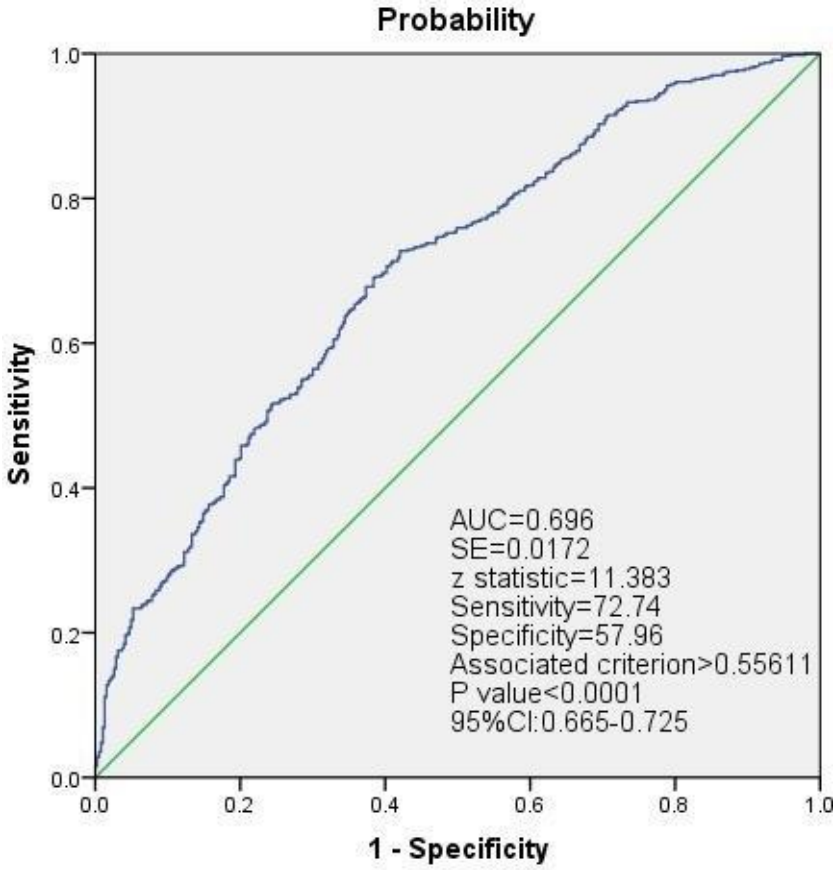
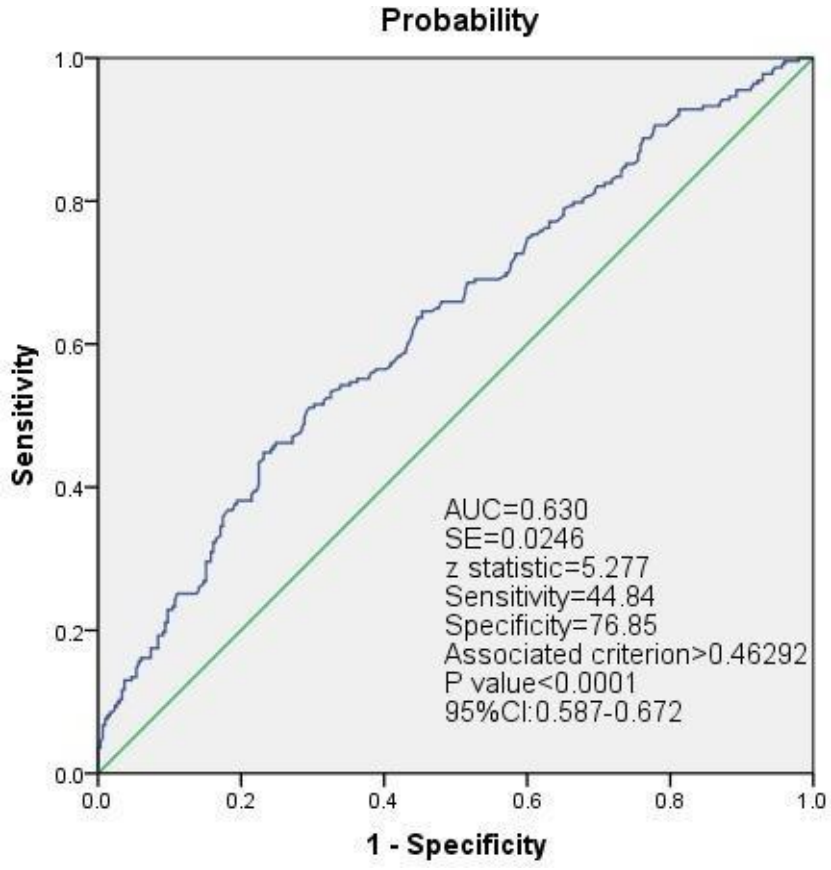


Figure 5 Receiver operating characteristic curve analyses for predicting LLNM in patients with and without MPTC and HT concurrently



Discussion

HT is a chronic inflammation of the thyroid gland that was initially described over a century ago but still has an incompletely defined etiopathogenesis[6]. It is now considered the most common autoimmune disease[4]often accompanied by diffuse lymphocyte infiltration,fibrosis, and parenchymal atrophy.HT is an autoimmune disease of the thyroid, and its own inflammation is closely related to the occurrence of tumors.Long-term infiltration of inflammation and damage to follicular epithelium may lead to the occurrence of tumors [15] .A large-cohort meta-analysis of recent studies concluded that HT is clearly associated with PTC [16].Some investigations have reported the genetic background of thyroid tumors with and without associated

autoimmunity, showing that the molecular features are significantly different in the two groups of PTCs (P = 0.001). Particularly in biomolecules, RET/PTC was more represented in patients with PTC and autoimmunity[17].

PTC, as the most common thyroid cancer,[1]is an indolent disease with a favorable prognosis, but there are still some patients with a poor prognosis, which is closely related to whether there is lymph node metastasis.PTC is the most important factor that increases the risk of local recurrence and overall survival[18][19].

Although the link between chronic inflammation and cancer is well established, the association between HT and PTC has been controversial in the literature since its initial description by Dailey et al. in 1955.Regarding the outcomes and clinical progression, a recent meta-analysis that included 71 published articles totaling 44,034 patients (of whom 11,132 had HT) showed a negative association between PTC with comorbid HT and aggressive behavior of cancer [20]. A study that retrospectively analyzed 305 patients revealed elevated incidence rates of PTC in patients with HT[25].

Multifocality is one of the clinicopathological features of tumors, and the diagnostic criteria are defined as the presence of ≥2 anatomically separated foci in the thyroid gland. Multifocality has been reported in 18% to 87% of patients with PTC[22]. Some studies have revealed that PTC with HT is more multifocal, and PTC patients with HT tend to exhibit multifocality (46.6% versus 21.6%, P < 0.001)[24], which means that PTC with HT should exhibit more lymph node metastasis. Amazingly, the result is the opposite, and many studies have proven that the coexistence of HT and

PTC appears to be associated with clinicopathological characteristics of reduced tumor aggressiveness and with diminished recurrence of the pathology,as particularly reported in [10]and[11]. A meta-analysis including 10 648 PTC cases showed that PTCs with coexisting HT were significantly related to the absence of lymph node metastasis (OR=1.3; P=0.041), and PTCs with HT were significantly associated with long recurrence-free survival (HR=0.6; P=0.001)[9]. Therefore, the outcome of lymph node metastasis in MPTC with HT is still unclear, and consequently, this study attempted to clarify its influence on lymph nodes and the importance of this mechanism.

In our study, 28% of all enrolled patients had combined HT, and 23.8% of them had MPTC. We also found that 158 MPTCs(40%) were confirmed at histological examination in patients with HT, while 178(17.5%)were confirmed in patients without HT(P＜0.001), which suggests that HT may predispose patients to the development of MPTC. No significant difference was found in lymph node metastasis. To determine the status of lymph node metastasis of MPTC combined with HT, we divided the patients into 2 groups based on the presence of HT and MPTC.The results in the HT group suggest that, there was no significant difference between MPTC and UPTC,whether in the CLN or the LLN. In contrast, compared with MPTC present without HT, MPTC combined with HT showed a lower CLNM(65.2% versus 93.3%, P < 0.001), number of metastatic CLNs(3.01±4.03 versus 5.16±4.36, P < 0.001），LLNM（58.6% versus 71.3% P=0.028）and number of metastatic LLNs(2.70±3.95 versus 3.93±4.88, P = 0.010).It seems that HT was a potential protective factor for reducing the risk of lymph node metastasis, which agrees with the conclusions of

most studies[25][27][28].This result may benefit from the immunologic response with a cancer-impeding effect of the lymphocytic infiltration in HT[29].When multifocality and HT existed at the same time, we found that the number of metastases of CLN or LLN was lower than that of UPTC without HT.(1.46±2.18 versus 2.09±3.00, p=0.042; 0.31±0.56 versus 1.43±2.57,p<0.001) and it seemed that the ability to promote lymph node metastasis of HT was stronger than that of MPTC. In addition, whether present in the whole population or in people with MPTC, the number of removed CLNs of patients with HT was more than that of patients without HT, which may suggest that patients with HT have more visible swollen lymph nodes during surgery, thereby proving the importance of intraoperative frozen-section examination. Therefore, unnecessary lymph node dissection was reduced to avoid serious complications after surgery that would affect the patient's quality of life.

Next, multivariate logistic regression analysis was performed in all patients(n=1413), patients with HT(n=395), patients with MPTC(n=336)and patients with and without HT and MPTC(n=998). In all patients,the presence of HT was noted as a protective factor for CLNM, however, in the univariate analysis, there was no obvious effect of HT on CLNM, which may be influenced by other factors. And multifocality was a risk factor for CLNM and LLNM, revealing that multifocality may increase the risk of lymph node metastasis in PTC with HT, same as the findings in most studies [12] [22][23].In addition,we found that the presence of HT was significantly associated with CLNM in patients with MPTC, suggesting that HT may decrease the risk of lymph node metastases. Then receiver operating characteristic

curves were constructed. Sex, age at diagnosis, tumor size, HT, multifocality, and number of removed CLNs were included to predict CLNM in all patients.Sex,age at diagnosis,HT, and number of removed CLNs were included to predict CLNM in patients with MPTC.Age at diagnosis,tumor size, multifocality and number of removed LLNs were included to predict LLNM in all patients(AUCs: 0.731, 0.842 and 0.690, respectively, $P < 0.0001$)(Figure 1, Figure 2 and Figure 3)

We also found that the new variable that indicates whether HT and MPTC exist at the same time was a protective factor in CLNM and LLNM（OR=0.502，95%CI=0.321-0.785，P<0.001 and OR=0.459, 95%CI=0.250-0.842，P<0.012）, which suggests that the two type of diseases may indirectly exert opposite effects and that the final effects may lead to a decrease in lymph node metastasis. Receiver operating characteristic curves were still uesed to predict CLNM and LLNM according to the status whether combined with HT and MPTC.(AUCs:0.696 and 0.630, P<0.0001)

HT is an autoimmune inflammatory disease that is considered to be related to PTC[25]. Chronic inflammation elicits an immune response leading to reactive alterations of stromal cells, genetic alterations,inappropriate cell proliferation and subsequent neoplastic transformation[29][30].Another hypothesis is that HT can cause hypothyroidism,resulting in increased TSH, which stimulates follicular epithelial proliferation and causes tumor progression [32]. To determine the relationship between HT and PTC, many studies have examined the biomolecular profiles between them and identified their common characteristics.The main molecular findings are

mutations in the oncogene BRAF (B-type Raf kinase)V600E and the recombination of RET/PTC (rearranged during transfection), andmany studies have revealed that RET/PTC oncogene rearrangements may be an early event in thyroid oncogenesis associated with HT[32]; this relationship had been demonstrated between the BRAF (V600E) mutationand HT. Catriona E Andersonet al revealed that HT may playa protective factor in PTCs by directly or indirectly inhibiting the expression of the BRAFV600E mutation and reducing the presence of aggressive factors in PTCs with the BRAFV600E mutation[33].Furthermore,CD98 expression and the P63 gene were found to be expressed in both PTC and HT[28][34], which may indicate a link between the two diseases.

For PTC, whether to perform lymph node dissection and how to choose the scope of dissection are very important, especially for prophylactic central neck dissection, and can increase the incidence of postoperative complications and decrease the patients' quality of life [35].Therefore, in the case of HT, which can reduce lymph node metastasis, when PTC is combined with HT, it is possible to further narrow the indications of prophylactic central neck dissection to achieve more accurate treatment and fewer complications. It is worth noting that we should pay more attention to multifocality when discovering HT because multifocality has a significant effect on lymph node metastasis.Our study show that the combination of HT and MPTC can lead to the decrease of CLNM compared with that without HT and

MPTC, but whether prophylactic central neck dissection must be performed still requires more research and experiments to prove its true clinical effect when surgeons discover HT or MPTC.

In conclusion, our results suggest that HT may predispose patients to the development of MPTC.HT is a protective factor in CLNM, and multifocality is a risk factor in CLNM and LLNM, when the two coexist, there is obvious protective effect on CLNM or LLNM. Therefore, these risk factors should be considered by surgeons when assessing a patient's condition preoperatively and intraoperatively.

Declaration: This study was approved by the ethical committees of the First Affiliated Hospital of Chongqing Medical University.There is no individual person's data in any form in this manuscript.

Data Availability: The data used to support the findings of this study are included within the supplementary information files.

Funding : This research did not receive any specific grant from any funding agency in the public, commercial or not-for-profit sector.

Conflict of interest: None.

Contributions:

Denghui Wang: data acquisition, analysis, drafted the manuscript and revised it.
Jiang Zhu, : data acquisition and revised.
Chang Deng : data acquisition.
Zhixin Yang : data acquisition.
Daixing Hu:revised.
Xiujie Shu:data acquisition.
Ping Yu:data acquisition.
Xinliang Su : examine and modify the manuscript.

REFERENCES

(1). W. Chen, R. Zheng, P. D. Baade, S. Zhang, H. Zeng, F. Bray, A. Jemal, X. Q. Yu and J. He.Cancer statistics in China, 2015. CA: a cancer journal for clinicians.

20 66(2016)115-32.

(2).Grodski S, Delbridge L. An update on papillary microcarcinoma.

Curr Opin Oncol. 2009;21:1---4.

(3)Davies L, Welch HG. Increasing incidence of thyroid cancer in the United States,

1973–2002. JAMA 2006;295:2164–7.

（4）McLeod DS, Cooper DS. The incidence and prevalence of thyroid autoimmunity.

En docrine 2012;42:252–65.

（5）Vanderpump MP, Tunbridge WM, French JM, Appleton D, Bates D, Clark F, et

al. The incidence of thyroid disorders in the community: a twenty-year follow-up of

the Whickham Survey. Clin Endocrinol (Oxf) 1995;43:55–68.

（6）Hashimoto H. Zur Kenntniss der lymphomatosen Verandderung

der Schilddruse (Struma Lymphomatosa). Arch Klin Chirurg.

1912;97:219---48.

（7）0Dailey ME, Lindsay S, Skahen R. Relation of thyroid neo

plasms to Hashimoto’s disease of the thyroid gland. Arch Surg.

1955;70:291---7.

（8）Salem I Noureldine,Ralph P TufanoAssociation of Hashimoto's Thyroiditis and

Thyroid Cancer[J] Curr Opin Oncol . 2015 Jan;27(1):21-5

（9）LEE J H, KIM Y, CHOI J W, et al. The association between papillary thyroid carcinoma and histologically proven Hashimoto's thyroiditis: a Meta-analysis［J］. Eur J Endocrinol, 2013, 168(3): 343-349.

(10)Kim EY, Kim WG, Kim WB, et al. Coexistence of chroniclymphocytic thyroiditis is associated with lower recurrence rates inpatients with papillary thyroid carcinoma. Clin Endocrinol.2009;71:581–586.

(11) J Liang , W Zeng ,.F Fang et al.Clinical Analysis of Hashimoto Thyroiditis Coexistent With Papillary Thyroid Cancer in 1392 Patients[J]Acta Otorhinolaryngol Ital . 2017 Oct;37(5):393-400

（12）Li Genpeng 1, Lei Jianyong 1 2, You Jiaying 2, Jiang Ke，et al.Independent Predictors and Lymph Node Metastasis Characteristics of Multifocal Papillary Thyroid Cancer。Medicine (Baltimore) 2018 Feb;97(5):e9619

(13)Schindler AM, van Melle G, Evequoz B, et al. Prognostic factors in papillary carcinoma of the thyroid. Cancer. 1991;68:324–330.

(14)Sciuto R, Romano L, Rea S, Marandino F, Sperduti I, Maini CL (2009) Natural history and clinical outcome of diferenti ated thyroid carcinoma: a retrospective analysis of 1503 patients treated at a single institution. Ann Oncol 20:1728–1735

（15）Guarino V, Castellone MD, Avilla E, Melillo RM. Thyroid cancer and inflammation. Mol Cell Endocrinol (2010) 321(1):94–102. doi:10.1016/j.mce.2009.10.003

(16)Lai X, Xia Y, Zhang B, Li J and Jiang Y. A meta-analysis of Hashimoto's thyroiditis and papillary thyroid carcinoma risk. Oncotarget 2017; 8: 62414-62424.

(17)Muzza M, Degl'Innocenti D, Colombo C, Perrino M, Ravasi E, Rossi S, CirelloV, Beck-Peccoz P, Borrello MG, Fugazzola L. The tight relationship between papillary thyroid cancer, autoimmunity and inflammation: clinical and molecular studies. Clin Endocrinol. 2010;72:702–8

(18) J. Lee, Y. Song and E. Y. Soh. Central lymph node metastasis is an important prognostic factor in patients with papillary thyroid microcarcinoma. Journal of Korean medical science. 29(2014)48-52.

(19)V. Zaydfudim, I. D. Feurer, M. R. Griffin and J. E. Phay. The impact of lymph node involvement on survival in patients with papillary and follicular thyroid carcinoma. Surgery. 144(2008)1070-7; discussion 7-8.

(20)Moon S, Chung HS, Yu JM, et al. Associations between Hashimoto Thyroiditis and Clinical Outcomes of Papillary Thyroid Cancer: A Meta-Analysis of Observational Studies. *Endocrinology and metabolism Seoul)* 2018;33: 473-484.

(21)Katoh R, Sasaki J, Kurihara H, Suzuki K, Iida Y, Kawaoi A 1992 Multiple thyroid involvement (intraglandular metastasis) in papillary thyroid carcinoma. A clinicopathologic study of 105 consecutive patients. Cancer 70:1585–90.

(22)Ayham Al Afif, Blair A Williams, Mathew H Rigby ,Martin J Bullock， S Mark Taylor, Jonathan Trites , Robert D Hart.Multifocal Papillary Thyroid Cancer Increases the Risk of Central Lymph Node Metastasis.Thyroid 2015 Sep;25(9):1008-12

(23)Tam AA, Özdemir D, Çuhacı N, et al. Association of multifocality, tumor number, and total tumor diameter with clinicopathological features in papillary thyroid cancer. Endocrine 2016;53:774–83.

(24) Feng Zhu , Yi Bin Shen, Fu Qiang Li, Yun Fang, et al.The Effects of Hashimoto Thyroiditis on Lymph Node Metastases in Unifocal and Multifocal Papillary Thyroid Carcinoma.Medicine (Baltimore).2016 Feb;95(6):e2674

（25）Giuseppa Graceffa , Renato Patrone , Salvatore Vieni, Silvia Campanella , Sergio Calamia et al.Association between Hashimoto's thyroiditis and papillary thyroid carcinoma: a retrospective analysis of 305 patients.BMC Endocr Disord. 2019 May 29;19(Suppl 1):26.

(26)Ju-Han Lee 1, Younghye Kim, Jung-Woo Choi, Young-Sik Kim.The Association Between Papillary Thyroid Carcinoma and Histologically Proven Hashimoto's Thyroiditis: A Meta-Analysis.Eur J Endocrinol. 2013 Feb 15;168(3):343-9.

(27)Jara SM, Carson KA, Pai SI, et al. The relationship between chronic lymphocytic thyroiditis and central neck lymph node metastasis in North American patients with papillary thyroid carcinoma. Surgery 2013; 154:1272–1280

(28)Jankovic B, Le KT, Hershman JM. Clinical review: Hashimoto's thyroiditis and papillary thyroid carcinoma: is there a correlation? J Clin Endocrinol Metab 2013; 98:474–482.

(29)Farrow B, Evers BM. Inflflammation and the development of pancreatic cancer.Surg Oncol 2002; 10:153–169.

(30)Buyukasik O, Hasdemir AO, Yalcin E, et al. The association between thyroid malignancy and chronic lymphocytic thyroiditis: should it alter the surgical approach? Endokrynol Pol 2011; 62:303–308.

(31)McLeod DS, Watters KF, Carpenter AD, et al. Thyrotropin and thyroid cancer diagnosis: a systematic review and dose-response meta-analysis. J Clin Endocrinol Metab 2012; 97:2682–2692

(32)Sheils OM, O'Eary JJ, Uhlmann V, et al. ret/PTC-1 activation in Hashimoto thyroiditis. Int J Surg Pathol 2000; 8:185–189.

(33)Rui-Chao Zeng ,Lang-Ping Jin, En-Dong Chen, Si-Yang Dong,et Potential Relationship Between Hashimoto's Thyroiditis and BRAF(V600E) Mutation Status in Papillary Thyroid Cancer.Head Neck 2016 Apr;38 Suppl 1:E1019-25

(34) vUnger P, Ewart M, Wang BY, et al. Expression of p63 in papillary thyroidcarcinoma and in Hashimoto's thyroiditis: a pathobiologic link? Hum Pathol2003; 34:764–769.

(35)Y. K. So, M. Y. Seo and Y. I. Son. Prophylactic central lymph node dissection for clinically node-negative papillary thyroid microcarcinoma: influence on serum thyroglobulin level, recurrencerate, and postoperative complications. Surgery. 151(2012)192-8.

Figures

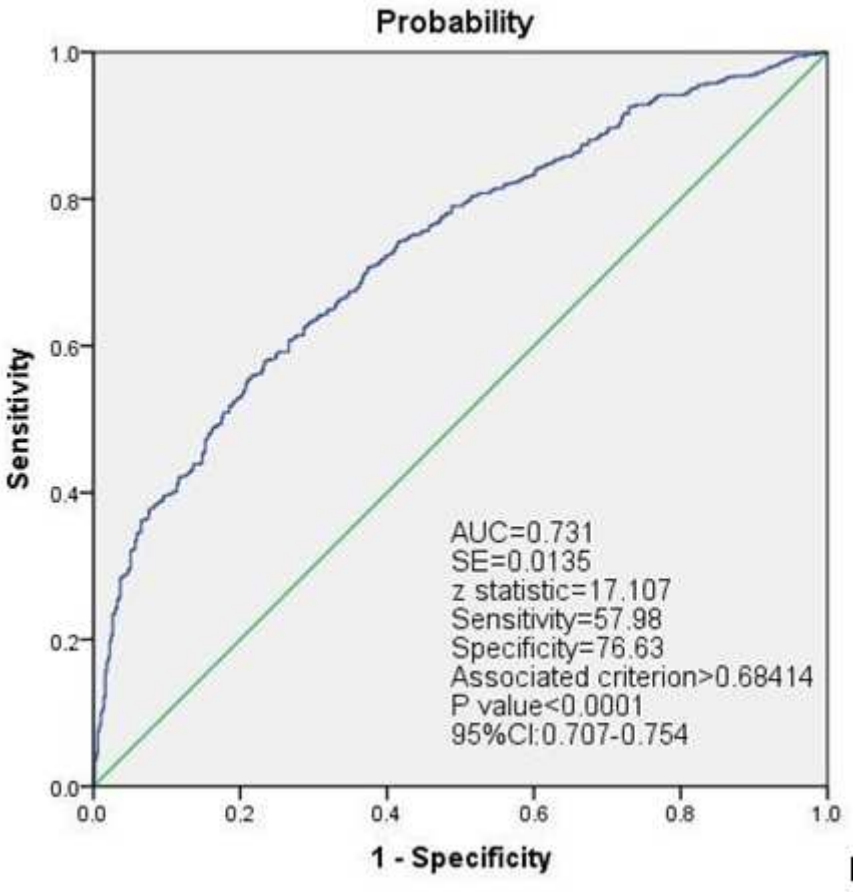


Figure 1

Receiver operating characteristic curve analyses for predicting CLNM in all patients

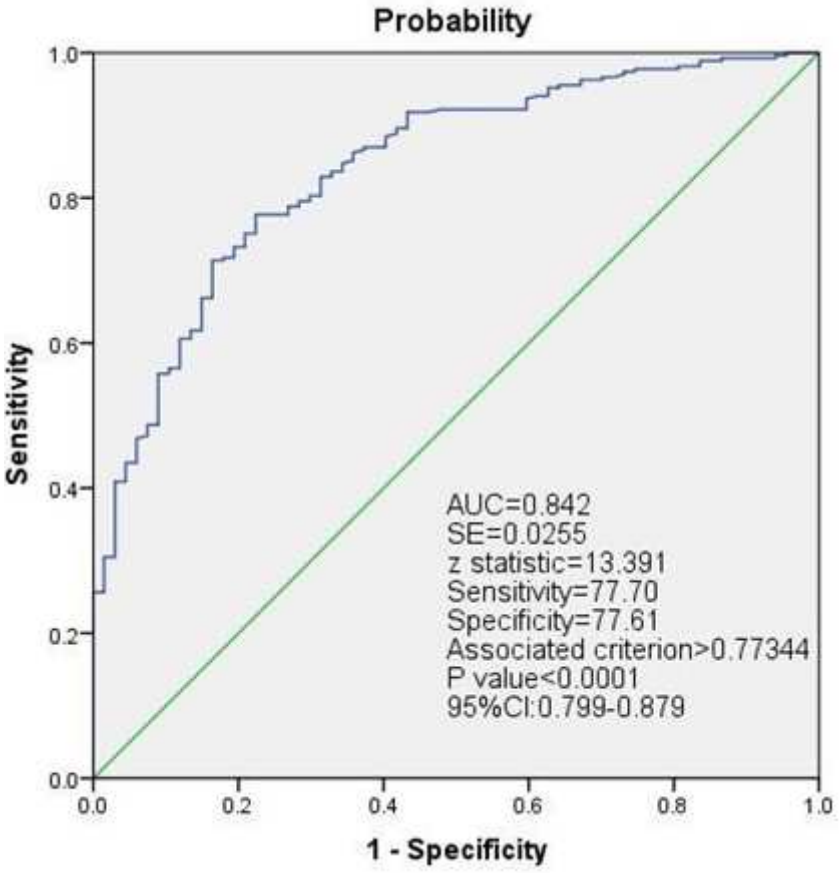


Figure 2

Receiver operating characteristic curve analyses for predicting CLNM in patients with MPTC.

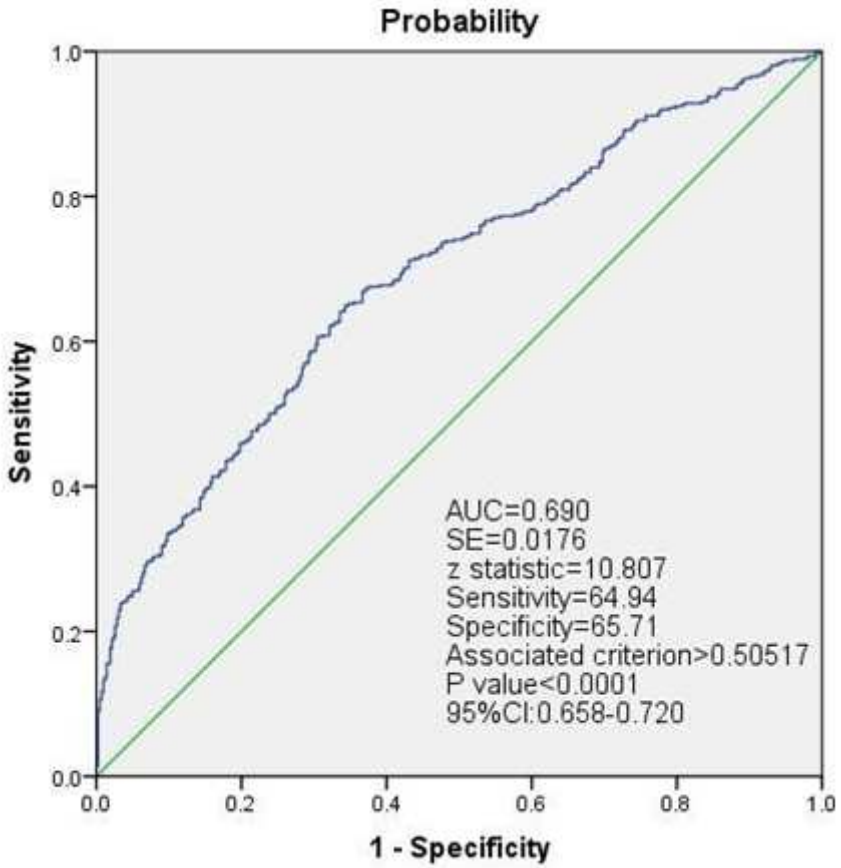


Figure 3

Receiver operating characteristic curve analyses for predicting LLNM in all

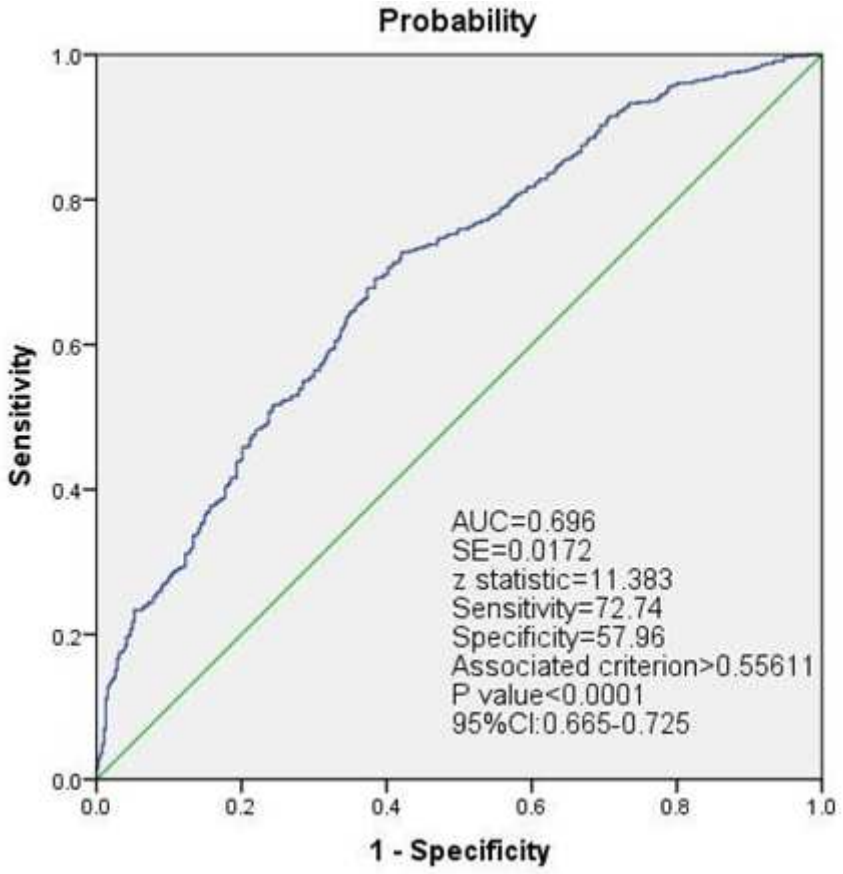


Figure 4

Receiver operating characteristic curve analyses for predicting CLNM in patients with and without MPTC and HT concurrently

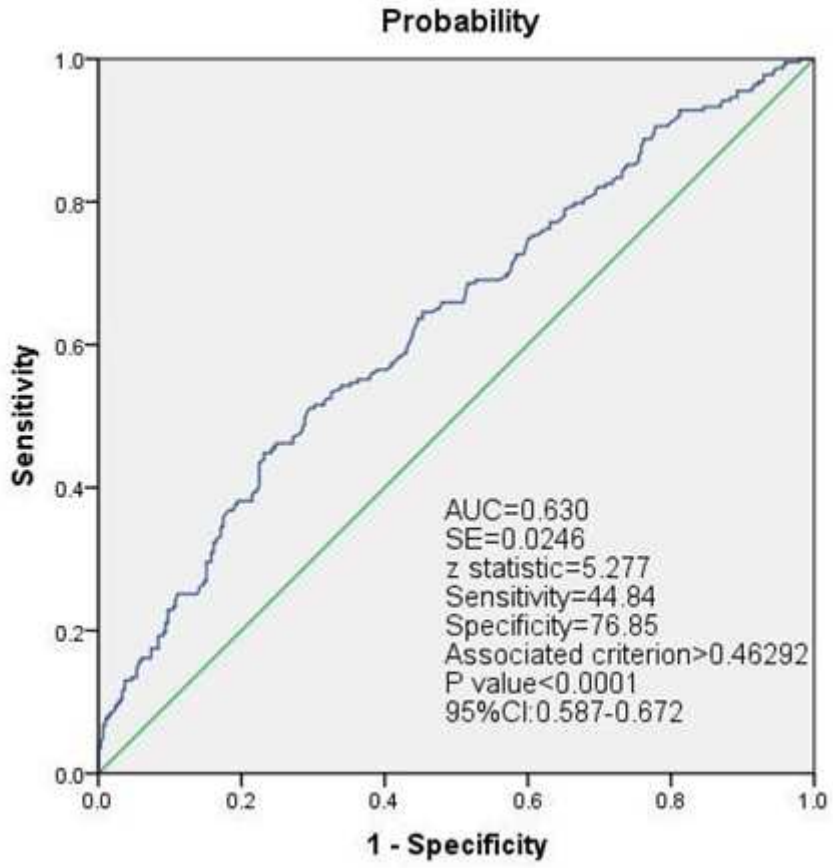


Figure 5

Receiver operating characteristic curve analyses for predicting LLNM in patients with and without MPTC and HT concurrently

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Data.pdf