Association between papillary thyroid carcinoma and lymphocytic thyroiditis: A retrospective study

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Abstract. The aim of the present study was to evaluate the association between coexisting lymphocytic thyroiditis (LT) and the clinicopathological features of papillary thyroid carcinoma (PTC). The records of 458 patients with PTC who underwent a total thyroidectomy and lymph node dissection in Sir Run Run Shaw Hospital (Hangzhou, China) were analyzed. In accordance with the histopathology of thyroid parenchyma, the cases were divided into three groups, including Hashimoto's thyroiditis (HT), non-Hashimoto's type LT (NHLT) and no LT. Based on the histopathology, data on age, sex, maximum diameter of tumor, multifocality, extrathyroidal extension, metastatic lymph node size, extranodal extension and tumor grades in the different groups were analyzed and compared. The prevalence of coexisting LT was 29.0% (133/458), of which 7.6% (35/458) was HT and 21.4% (98/458) was NHLT. PTC concomitant with LT was significantly associated with female patients (95.5 vs. 70.2%; P<0.001), a lower rate of extra-thyroidal extension and/or capsular invasion (25.6 vs. 39.7%; P=0.004), central lymph node metastasis (CLNM) ratio (10.71 vs. 17.37; P=0.014), higher number of dissected central lymph nodes (16.83 vs. 11.7; P<0.001), larger metastatic lymph nodes (0.66 vs. 0.46 cm; P<0.001), higher occurrence of multifocality (61.7 vs. 50.5%; P=0.029) and earlier pT stage (57.9 vs. 38.8%; P<0.001), regardless of the combined or separate consideration of HT and NHLT. Besides, LT was associated with multifocality [odds ratio (OR), 1.578; 95% confidence interval (CI), 1.046-2.382; P=0.030]. Furthermore, in patients with PTC, CLNM had a significant association with the male sex (OR, 2.000; 95% CI, 1.216-3.288; P=0.006), an age of <45 years (OR, 0.592; 95% CI, 0.398-0.879; P=0.009) and a tumor size of >1 cm (OR, 3.913; 95% CI, 2.431-5.734; P<0.001). In conclusion, patients with PTC and LT showed a greater female preponderance, multifocality, a lower extrathyroidal extension and a lower CLNM ratio. LT was associated with an increased risk of multifocality in PTC.

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Introduction

Papillary thyroid carcinoma (PTC) coexisting with Hashimoto's thyroiditis (HT) currently remains a research hotspot and is controversial. The coexistence was first reported by Dailey *et al* (1) in 1955, and a vast number of studies subsequently explored the epidemiology and etiology of the concurrent diseases (2-4). However, the precise pathogenesis of these diseases arouses a fierce argument.

A number of studies demonstrated that HT was significantly associated with the prevalence of PTC (2,3,5). Numerous studies also indicated that patients with PTC and HT were associated with a better prognostic outcome, such as a smaller tumor size and lower tumor grade. HT in patients with PTC was also associated with better locoregional control, a lower recurrence rate and a greater survival rate (6,7). As for this favorable prognosis, one hypothesis suggested that the immune response of lymphocytic infiltration in patients with PTC plays a vital role in controlling tumor growth and proliferation (8). Conversely, it was reported that the co-occurrence of HT and PTC showed no protection of patient outcome (5), while another study suggested that patients with PTC and lymphocytic thyroiditis (LT) were associated with multifocal involvement (7).

Numerous investigators have reported that clinicopathological features, such as tumor size, multifocality, capsular invasion and central lymph node metastasis (CLNM), are associated with the prognosis of PTC (5,9,10). Nevertheless, there are few published studies with regard to the association between coexisting HT and PTC tumor grades, bilaterality, multifocality and especially histological CLN characteristics (size, number and extranodal extension) using the histopathological results (2). To investigate whether the coexistence of LT or HT in patients with PTC may result in a better outcome, the present study was conducted to assess the prevalence of coexistent LT or HT in patients who received thyroid surgery

for PTC in a retrospective cohort. The study also explored the association between LT or HT in patients with PTC and clinicopathological features. Furthermore, the study sought to investigate the potential risk factors of the prognosis of PTC, especially multifocality PTC (MPTC) with coexistent LT.

Materials and methods

Patients. A total of 458 patients with primary PTC who underwent initial total thyroidectomy surgery with therapeutic or prophylactic central lymph node dissection (LND) (398 patients) or lateral LND (60 patients) between January 2012 and December 2014 in Sir Run Run Shaw Hospital (Hangzhou, China) were included in the present study. This retrospective study was approved by the Ethics Committee of Sir Run Run Shaw Hospital, Zhejiang University School of Medicine (Hangzhou, China). All patients provided written informed consent before the study. The inclusion criteria were patients with primary PTC and a complete a medical history, excluding those with a previous thyroidectomy, and excluding incidental PTC during thyroid surgery for benign neoplasms (without neck dissection).

Examinations. All patients received a preoperative evaluation, including a physical examination, laboratory tests and an imaging examination. Initial assessment was conducted by routine physical examination and ultrasonography (US) of the thyroid and neck lymph nodes (central and lateral). After an abnormal finding and a suspected tumor on US, an US-guided fine-needle aspiration (FNA) was performed to further acquire the pathological diagnosis of the suspicious lesions. For the patients with lateral neck lymph node metastasis, computed tomography of the thyroid was performed and the scanning range was from the mastoid of the temporal bone to the innominate artery. Laryngoscopy was used to evaluate the function of the vocal cord. In addition, blood tests, including tests for thyroid and parathyroid hormones, calcitonin and serum calcium levels, were also performed. The serological detection of thyroglobulin antibody (TG-Ab), thyroid peroxidase antibody (TPO-Ab) and thyroid-stimulating hormone (TSH) were conducted uing a full-automatic chemiluminescence analyzer.

Thyroid surgery. A total thyroidectomy was conducted according to the guidelines of the American Thyroid Association (11). For patients with PTC, an ipsilateral central neck dissection (CND) is routinely performed in Sir Run Run Shaw Hospital. Once the isthmuses located in the lesion or malignant nodules were found in both lobes, a bilateral CND was conducted. If the patients with PTC had clinical evident nodal disease or FNA of a lateral node was indicated to be malignant, a modified lateral neck dissection (levels II-IV) was chosen. All operations included were performed as conventional open surgery by the surgeons of the same medical group.

Tumor grade. Tumor grade was in accordance with the 7th American Joint Committee on Cancer Tumor-Node-Metastasis (AJCC TNM) stage (12). For T stage of PTC, maximum diameter of a primary PTC and depth of tumor invasion (intraglandular or extraglandular, such as extrathyroidal fat, adjacent strap muscle, tracheal, esophageal or carotid wall) are used to divided PTC into 5 stages (T1a, T1b, T2, T3 and T4). With regard to N stage, there are 3 stages: N0 is without nodal metastasis; N1a refers to CLNM; and N1b indicates PTC metastasis to the regional node(s). The definition of multifocality or bilaterality was the presence of more than one tumor foci within a PTC or PTC in both thyroid lobes, respectively. There was no distant metastasis in any of the patients.

Clinicopathological factors. According to the histopathological results, thyroid parenchyma was divided into two types through diffuse infiltration of lymphocytes and inflammatory cells in the thyroid gland, and included LT and no LT. LT was further classified as HT and non-Hashimoto's type LT (NHLT). HT has a progressive loss of thyroid follicular cells and the presence of germinal centers associated with fibrosis.

Statistical analysis. All data, including tumor characteristics and clinicopathological features, were collated in Microsoft Excel 2021 (Microsoft Corporation). In accordance with thyroid parenchyma in tumor characteristics, different analyses were conducted to compare the clinicopathological features between two groups (PTC without LT and PTC with LT), and among three groups (PTC without LT, PTC with HT, and PTC with NHLT). When comparing two groups, the unpaired Student's t-test, χ^2 test, Fisher's exact test and Wilcoxon's rank sum test were used. One-way ANOVA was performed for three groups when data met the requirements of homogeneity of variance and Kruskal-Wallis test was performed when the requirements were not met. Univariate and multivariate logistic regression analyses were performed to identity candidate risk factors. An independent samples t-test was used for TG-Ab, TPO-Ab and TSH in the comparison between PTC with HT and PTC with NHLT. SPSS 18.0 (IBM Inc.) was used to conduct data analyses. $P<0.05$ was considered to indicate a statistically significant difference.

Results

Comparisons of the clinicopathological features. The age of the 458 patients ranged from 13 to 78 years, with a mean age of 43.9±11.2 years. With regard to the sex preponderance of all the patients, there were more women than men [77.5% (355/458) vs. 22.5% (103/458); Table I]. Overall, two different surgical operations were conducted: i) Total thyroidectomy (including isthmectomy and pyramidal lobectomy) with ipsilateral CND; and ii) total thyroidectomy with bilateral CND. The number of coexistent LT cases among the 458 patients with PTC was 133 (29.0%), of which 35 patients (7.6%) were classified as HT and 98 (21.4%) were classified as NHLT (Table II).

LT and PTC. At the beginning, all 458 patients with PTC were divided into two groups, PTC without LT and PTC with LT. Based on this grouping method, statistical analyses were conducted using the unpaired Student's t-test, the χ^2 test, Fisher's exact test and Wilcoxon's rank sum test. Compared to PTC without LT, the predominance of PTC with LT was higher in women ($P<0.001$; Table I). The prevalence of extrathyroidal extension and/or capsular invasion was significantly higher in patients without LT ($P=0.004$; Table I). A larger dissected CLN number was evident in

Table I. Clinicopathological features of patients with PTC with LT (n=133) and without LT (n=325).

Parameters	PTC without LT	PTC with LT	P-value
Sex, n (%)			<0.001
Female	228 (70.2)	127 (95.5)	
Male	97 (29.8)	6 (4.5)	
Age, years[a]	44.32±11.34	42.62±10.88	0.291
Maximum diameter, cm[a]	10.27±6.31	9.52±6.45	0.086
Focality, n (%)			0.029
Unifocal	161 (49.5)	51 (38.3)	
Multifocal	164 (50.5)	82 (61.7)	
Multifocal, n (%)			0.267
Ipsilateral	49 (15.1)	19 (14.3)	
Bilateral	115 (35.4)	63 (47.4)	
Extrathyroidal extension and/or capsular invasion, n (%)			0.004
No	196 (60.3)	99 (74.4)	
Yes	129 (39.7)	34 (25.6)	
CLNM and LLNM, n (%)			0.436
No	141 (43.4)	63 (47.4)	
Yes	184 (56.6)	70 (52.6)	
CLNM, n (%)			0.329
No	145 (44.6)	66 (49.6)	
Yes	180 (55.4)	67 (50.4)	
CLNM number[a]	2.07±2.84	1.68±2.65	0.157
Dissected CLN number[a]	11.71±5.64	16.83±6.96	<0.001
CLNM ratio[a]	17.37±21.75	10.71±16.27	0.014

[a]Values are presented as the mean ± standard deviation. PTC, papillary thyroid carcinoma; CLN, central lymph node; CLNM, CLN metastasis; LT, lymphocytic thyroiditis; LLNM, lateral lymph node metastasis; CLNM ratio, central metastatic lymph node number/central dissected lymph node number.

the PTC with LT group (P<0.001; Table I), while the CLN metastasis ratio (metastatic CLN number/dissected CLN number) in PTC with LT was significantly lower than that in PTC without LT (P=0.014; Table I). Compared to patients with PTC without LT, patients with PTC and LT had the tendency to present with multifocality (61.7 vs. 50.5%, P=0.029; Table I) and bigger metastatic lymph nodes (0.66 vs. 0.46 cm; P<0.001; Table III), and LT was associated with multifocality [odds ratio (OR), 1.578; 95% confidence interval (CI), 1.046-2.382; P=0.030; Table IV). However, there was no significant difference in the prevalence of age, maximum diameter and the location of multifocality (ipsilateral or bilateral) between the two groups (P=0.291, P=0.086 and P=0.267 respectively). Meanwhile, the CLNM alone and the CLNM number also exhibited no significant differences between the two groups (P=0.329 and P=0.157, respectively; Table I). With regard to pathological tumor (pT) staging, the group with coexisting LT exhibited a higher incidence of pT1a stage disease (57.9 vs. 38.8%; P<0.001) and a lower incidence of pT1b (15.0 vs. 18.7%; P<0.001), pT2 (1.5 vs. 3.7%; P<0.001), pT3 (19.6 vs. 28.9%; P<0.001) and pT4 (6.0 vs. 9.9%; P<0.001) stage disease (Table V). There was no difference in the distribution of pathological nodal staging and AJCC staging.

HT and PTC. To determine the characteristics of HT, the 458 patients with PTC were further classified into three groups: PTC without LT, PTC with HT and PTC with NHLT. Comparisons between groups were performed using one-way ANOVA or Kruskal-Wallis tests. As shown in Table II, significant differences among the three groups with regard to sex (P<0.001), extrathyroidal extension and/or capsular invasion (P=0.004), dissected CLN number (P<0.001) and CLNM ratio (P=0.009) were observed. Although the patients with PTC and coexisting LT were divided into those with HT and NHLT, there was no significant difference between patients with no LT and those with coexistent LT with respect to age, maximum diameter, bilaterality (Table II), N stage and AJCC stage (Table VI), as well as those with extranodal extension (Table VII). Additionally, the TG-Ab and TPO-Ab values in patients with PTC and HT were significantly increased compared with those in patients with PTC and NHLT (P<0.011 and P<0.002, respectively). The TSH level of patients with PTC and HT tended to be lower, but this difference was not statistically significant (P=0.727) (Table SI).

Risk factors for lymph node metastases in PTC. The five factors (sex, age, tumor size, LT presence and multifocality) were included to perform a multivariate logistic regression analysis. The male sex (OR, 2.000; 95% CI, 1.216-3.288; P=0.006), an

Table II. Clinicopathological features of PTC with HT (n=35) or NHLT (n=98), and without LT (n=325).

Parameters	PTC without LT	PTC with HT	PTC with NHLT	P-value
Sex, n (%)				<0.001
Female	228 (70.2)	33 (94.3)	94 (95.9)	
Male	97 (29.8)	2 (5.7)	4 (4.1)	
Age, years[a]	44.32±11.34	42.66±11.56	42.60±10.69	0.321
Maximum diameter, cm[a]	10.27±6.31	8.63±4.58	9.83±7.00	0.078
Focality, n (%)				0.090
Unifocal	161 (49.5)	14 (40.0)	37 (37.8)	
Multifocal	164 (50.5)	21 (60.0)	61 (62.2)	
Multifocal, n (%)				0.145
Ipsilateral	49 (15.1)	2 (5.7)	17 (17.3)	
Bilateral	115 (35.4)	19 (54.3)	44 (44.9)	
Extrathyroidal extension and/or capsular invasion, n (%)				0.004
No	196 (60.3)	30 (85.7)	69 (70.4)	
Yes	129 (39.7)	5 (14.3)	29 (29.6)	
CLNM and LLNM, n (%)				0.630
No	141 (43.4)	18 (51.4)	45 (45.9)	
Yes	184 (56.6)	17 (48.6)	53 (54.1)	
CLNM, n (%)				0.504
No	145 (44.6)	19 (54.3)	47 (48.0)	
Yes	180 (55.4)	16 (45.7)	51 (52.0)	
CLNM number[a]	2.07±2.84	1.29±1.90	1.83±2.87	0.132
Dissected CLN number[a]	11.71±5.64	17.97±8.60	16.42±6.27	<0.001
CLNM ratio[a]	17.37±21.75	10.24±18.30	10.88±15.58	0.009

[a]Values are presented as the mean ± standard deviation. PTC, papillary thyroid carcinoma; LT, lymphocytic thyroiditis; HT, Hashimoto's thyroiditis; NHLT, non-Hashimoto's type LT; CLN, central lymph node; CLNM, CLN metastasis; LLNM, lateral lymph node metastasis; CLNM ratio, central metastatic lymph node number/central dissected lymph node number.

Table III. Clinicopathological features of metastatic lymph nodes in patients with PTC with (n=58) and without (n=158) LT.

Parameters	PTC without LT	PTC with LT	P-value
Size of metastatic lymph nodes, cm[a]	0.46	0.66	<0.001
Extranodal extension, n (%)			0.189
Yes	32 (20.3)	8 (13.8)	
No	126 (79.7)	50 (86.2)	

[a]Values are presented as the mean. PTC, papillary thyroid carcinoma; LT, lymphocytic thyroiditis.

age of <45 years (OR, 0.592; 95% CI, 0.398-0.879; P=0.009) and a tumor diameter >1 cm (OR, 3.913; 95% CI, 2.431-5.734; P<0.001) were significantly associated with CLNM in patients with PTC (Table VIII).

Discussion

LT is widely acknowledged as an autoimmune thyroid disease that contains a common form of chronic lymphocytic thyroiditis, also known as HT, which was first described by Hakaru Hashimoto in 1912 (13). HT exhibits an association with thyroid dysfunction and the development of thyroid nodules. Currently, PTC is the most common type of thyroid carcinoma, with an incidence rate that has risen markedly in recent years (14). However, the overall cancer-related 10-year survival rate for PTC after surgery and radioactive iodide treatment has reached nearly 90% (15).

Since Dailey *et al* (1) first found the association between HT and thyroid carcinoma in 1955, debate has risen about the association between PTC and HT. A study by de

Table IV. Multivariate logistic regression analysis for multifocality papillary thyroid carcinoma.

Variables	OR	95% CI	P-value
Sex (male)	0.846	0.545-1.313	0.456
Age (<45 years)	1.190	0.822-1.723	0.357
LT (present)	1.578	1.046-2.382	0.030

LT, lymphocytic thyroiditis; OR, odds ratio; CI, confidence interval.

Alcântara-Jones *et al* (16) declared that there was no association between HT and PTC, which was similar to the finding in the study by Anil *et al* (17). Although rarely seen in daily clinical activities, the coexistence of HT in patients with thyroid carcinoma has increased gradually, with a prevalence varying from 9 to 58%, and the mean age of patients being affected ranging from 39.5 to 69.0 years (2), depending on different regions and ethnicities. Di Pasquale *et al* (18) showed that out of 33 patients with HT who underwent long-term follow-up, there were 33 cases with coexisting thyroid carcinoma, including 30 PTCs. Similar results were reported in the study by Intidhar *et al* (19), where PTC in patients with HT accounted for 14% of cases, and the meta-analysis further identified that the rate of HT coexisting with PTC was higher than coexistence with benign thyroid disease or other thyroid cancer types (2). The present study found that the prevalence of LT in patients with PTC was 29.0%, while the prevalence of HT was 7.6%. The finding suggested that HT might contribute to be a risk factor for PTC (2), as also indicated in a hypothesis that HT refers to a chronic inflammatory disorder and long persistent inflammatory stimulation to generate a higher serum TSH level, which contributes to the development of PTC (3,20).

To date, the association between coexisting HT with PTC and clinical prognosis remains controversial. A number of studies have suggested that patients with PTC coexisting with HT could exhibit a better prognosis than those with PTC without HT. In a meta-analysis, Lee *et al* (2) considered that PTCs with coexistent HT had a tight association with a number of factors, such as the female sex, multifocality and high recurrence-free survival rates, which was confirmed in a study by Huang *et al* (21), which suggested that HT coexisting with PTC is associated with a favorable prognosis. Moreover, previous studies indicated that lymphocytic infiltration led to a low frequency of recurrence and an improvement in disease-free survival rate (22,23). However, the higher rate of multifocality (24) in LT-associated PTC cases raises the opposite view due to its tendency to result in a poor prognosis. It was previously reported by Del Rio *et al* (25) that HT had no effect on the aggressiveness of PTC. With regard to the present study, PTC concomitant with LT was associated with the female sex, a low capsular invasion rate and a low CLNM ratio, but larger metastatic lymph nodes and a higher rate of multifocality. The reasons for these differences could partly be explained by variations in the study design, or the variability of patients with PTC coexisting with LT and different multifocal forms of PTC.

Table V. T and N stage in the comparison between patients with PTC with (n=133) and without (n=325) LT.

Parameters	PTC without LT	PTC with LT	P-value
T stage, n (%)			
T1a	126 (38.8)	77 (57.9)	<0.001
T1b	61 (18.8)	20 (15.0)	<0.001
T2	12 (3.7)	2 (1.5)	<0.001
T3	94 (28.9)	26 (19.6)	<0.001
T4	32 (9.8)	8 (6.0)	<0.001
N stage, n (%)			0.721
N0	142 (43.7)	63 (47.4)	
N1a	144 (44.3)	51 (38.3)	
N1b	39 (12.0)	19 (14.3)	
AJCC stage, n (%)			0.454
I	221 (68.0)	96 (72.2)	
II	4 (1.2)	0 (0.0)	
III	79 (24.3)	28 (21.1)	
IV	21 (6.5)	9 (6.7)	

PTC, papillary thyroid carcinoma; LT, lymphocytic thyroiditis; T, tumor; N, nodal; AJCC, American Joint Committee on Cancer.

Despite the fact that few published studies have demonstrated the associations between metastatic lymph node size in patients with PTC with or without LT, the present study found that LT in patients with PTC was associated with larger metastatic lymph nodes, contrary to the low CLNM ratio. Metastatic lymph nodes often enlarge due to an immune reaction to various stimuli in thyroid carcinoma and lymphocytic thyroiditis. Sugitani *et al* (26) and Randolph *et al* (27) identified that larger lymph nodes (>3 cm in diameter) have a higher risk of recurrence. However, a challenging study also indicated that small lymph nodes are at risk of harboring aggressive disease biology (28). It still remains unknown as to whether large metastatic lymph nodes can have adverse histological features.

The specific mechanism between HT in PTC and the host immune reaction remains unclear (21). It was reported that the balance between pro-inflammatory and anti-inflammatory factors, including IL-4 and IL-6, in PTC with HT is disrupted, which has a tendency to exacerbate the autoimmune response (29). However, the main molecular findings involved in this autoimmune response are the mutation of the BRAF oncogene, the rearrangement of RET/PTC and the expression of p63. Previous studies revealed a high prevalence of the $BRAF^{V600E}$ mutation in PTC lymph node metastasis, although the association between the two remains unknown (30). Furthermore, studies by Wirtschafter *et al* (31) and Arif *et al* (32) identified expression of the RET/PTC fusion gene rearrangements in patients with HT. Similarly, Bozec *et al* (33) indicated that HT might play an important role in the MAPK signaling pathway for PTC. Moreover, p63 expression documented by Unger *et al* (34) seemed to be commonly expressed in PTC and in HT, which was further confirmed by Burstein *et al* (35).

Table VI. T and N stage of PTC in patients with HT (n=35) or NHLT (n=98) and without LT (n=325).

Parameters	PTC without LT	PTC with HT	PTC with NHLT	P-value
T stage, n (%)				0.001
T1a	126 (38.8)	23 (65.7)	54 (55.1)	
T1b	61 (18.7)	7 (20.0)	13 (13.3)	
T2	12 (3.7)	0 (0.0)	2 (2.0)	
T3	94 (28.9)	5 (14.3)	21 (21.4)	
T4	32 (9.8)	0 (0.0)	8 (8.2)	
N stage, n (%)				0.667
N0	142 (43.7)	17 (48.6)	46 (46.9)	
N1a	144 (44.3)	15 (42.9)	36 (36.8)	
N1b	39 (12.0)	3 (8.6)	16 (16.3)	
AJCC stage, n (%)				0.539
I	221 (68.0)	23 (65.7)	73 (74.5)	
II	4 (1.2)	0 (0.0)	0 (0.0)	
III	79 (24.3)	11 (31.4)	17 (17.3)	
IV	21 (6.5)	1 (2.9)	8 (8.2)	

PTC, papillary thyroid carcinoma; LT, lymphocytic thyroiditis; HT, Hashimoto's thyroiditis; NHLT, non-Hashimoto's type LT.

Table VII. Clinicopathological features of metastatic lymph nodes in patients with HT (n=14) or NHLT (n=44) and without LT (n=158).

Parameters	PTC without LT	PTC with HT	PTC with NHLT	P-value
Size of metastatic lymph nodes, cm[a]	0.46	0.71	0.65	<0.001
Extranodal extension, n (%)				0.169
Yes	32 (20.3)	2 (14.3)	6 (13.6)	
No	126 (79.7)	12 (85.7)	38 (86.4)	

[a]Values are presented as the mean. PTC, papillary thyroid carcinoma; LT, lymphocytic thyroiditis; HT, Hashimoto's thyroiditis; NHLT, non-Hashimoto's type LT.

Table VIII. Multivariate logistic regression analysis for central lymph node metastasis.

Variables	OR	95% CI	P-value
Sex (male)	2.000	1.216-3.288	0.006
Age (<45 years)	0.592	0.398-0.879	0.009
Tumor diameter (>1 cm)	3.913	2.431-5.734	<0.001
Multifocality (present)	0.294	0.567-1.187	0.294
LT (present)	0.851	0.568-1.277	0.436

LT, lymphocytic thyroiditis; OR, odds ratio; CI, confidence interval.

Some of the cases of PTC present with tumor multifocality, with a prevalence that varies from 18 to 87% (36,37). Most cases of MPTC consist of a major lesion accompanied by some nodules, while others are of diffuse microcarcinomas. It was previously reported that MPTC could be more commonly observed in PTC coexistent with LT than solitary PTC (38). The present study documented a significantly higher occurrence of multifocal tumors among patients with concomitant LT, and LT was significantly associated with multifocality (OR, 1.578; 95% CI, 1.046-2.382; P=0.030), which was a similar result to that found by Asanuma *et al* (39). By contrast, some studies indicated a higher rate of HT in patients with MPTC (40). However, the association between coexisting HT with PTC or MPTC remains controversial. Jeong *et al* (5) found that the coexistence of LT in patients with PTC did not affect multifocality. A study suggested that HT might contribute to the development of MPTC through the change in the environment of the gland due to the inflammation (8). Tumor-associated LT is frequently observed in the tumor microenvironment of PTC. In HT, infiltration of lymphocytes results in destruction of the thyroid tissue and consequent hypothyroidism, while in PTC with LT, there is not usually an association with the development of concurrent

hypothyroidism (41). In the present study, LT was defined as a diffuse infiltration of lymphocytes and inflammatory cells in the thyroid parenchyma, and HT was a progressive loss of thyroid follicular cells and the presence of germinal centers associated with fibrosis. These definitions suggest that the thyroid follicular cells in PTC with HT have progressive and caused further injury. Additionally, it was found that multifocality were more frequently observed in patients with PTC and LT than in those with PTC without LT. Therefore, it is important for doctors to pay more attention to observe the tumor multifocality in PTC coexisting with LT in the process of the operative examination, and a more aggressive surgery and postoperative monitoring are necessary.

The present study plainly indicated that multifocality was not a significant risk factor of CLNM. Multifocality was previously reported as a factor for aggressive disease in PTC (42), while other studies showed a significant difference between unifocality and multifocality in patients with PTC (43). However, Sherman *et al* (44) believed that the multifocality of PTC was associated with unfavorable outcomes. In the retrospective study by Kuo *et al* (45), multifocal PTC had a higher rate of lymph node metastases, and easily presented with soft-tissue invasion and distant metastases compared with unifocal PTC. This was confirmed in the study by Kim *et al* (46), which found that multifocal PTC was associated with cervical lymph node metastasis, extrathyroidal extension and advanced TNM stage. Furthermore, Qu *et al* (47) and Hay *et al* (48) revealed that multifocal tumors were more prone to relapse compared with unifocal tumors. Most recently, Al Afif *et al* (49) demonstrated that the number of tumor foci for PTC was positively associated with the metastasis rate when the number was >2 foci. In conclusion, tumor foci could be used as a risk factor for a poorer prognosis. Therefore, it is necessary for the surgeon to conduct more detailed imaging tests and an FNA biopsy to confirm the multifocality of a lesion, and to pay more attention to tumor multifocality during the therapy of PTC with coexistent LT.

The present study had several limitations. First, the study was retrospective study and from a single center, whereas a multicenter prospective study would be more convincing. Second, further experimental studies should be performed to evaluate the mechanism of the molecular biology. Third, the prognoses of patients with PTC were not documented in the study, and more information might indicate the effect of HT. Finally, the study found that LT was associated with a reduced risk of CLNM; nevertheless, the influence of larger metastatic lymph nodes and a tendency for multifocality remain unknown.

In conclusion, the present study provided an analysis of the association between LT and PTC. The findings demonstrated that PTC concomitant with LT was associated with the female sex, a lower capsular invasion rate, a lower CLNM ratio, larger metastatic lymph nodes and a tendency for multifocality, thus indicating the complexity of the effect of LT on PTC prognosis.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

LX and KW designed the study. KW, LS and JW collected the data and performed the analysis. All authors contributed to the manuscript and approved the submitted version. LX and KW confirm the authenticity of all the raw data. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

This study was approved by the Ethics Committee of Sir Run Run Shaw Hospital, Medical School of Zhejiang University (Hangzhou, China; approval no. 20200716-019). Written informed consent was obtained from all patients before the study.

Patient consent for publication

Written informed consent was obtained from all patients before the study.

Competing interests

Not applicable.

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