

# Pathologic Spectrum of Lymphocytic Infiltration and Recurrence of Papillary Thyroid Carcinoma

Hyun Gi Kim,<sup>1</sup> Eun-Kyung Kim,<sup>1</sup> Kyung Hwa Han,<sup>2</sup> Hyunki Kim,<sup>3</sup> and Jin Young Kwak<sup>1</sup>

Departments of <sup>1</sup>Radiology and <sup>3</sup>Pathology, Research Institute of Radiological Science, Severance Hospital, Yonsei University College of Medicine, Seoul; <sup>2</sup>Biostatistics Collaboration Unit, Medical Research Center, Yonsei University College of Medicine, Seoul, Korea.

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Co-corresponding authors: Dr. Jin Young Kwak,

Department of Radiology,

Research Institute of Radiological Science,

Severance Hospital,

Yonsei University College of Medicine,

50-1 Yonsei-ro, Seodaemun-gu,

Seoul 120-752, Korea.

Tel: 82-2-2228-7413, Fax: 82-2-393-3035

E-mail: docjin@yuhs.ac and

Dr. Hyunki Kim,

Department of Pathology,

Research Institute of Radiological Science,

Severance Hospital,

Yonsei University College of Medicine,

50-1 Yonsei-ro, Seodaemun-gu,

Seoul 120-752, Korea.

Tel: 82-2-2228-1764, Fax: 82-2-362-0860

E-mail: kimhyunki@yuhs.ac

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**Purpose:** The aim of this study was to investigate the prognosis of papillary thyroid carcinoma (PTC) patients according to different pathologic grades of lymphocytic thyroiditis (LT). **Materials and Methods:** This study included 144 PTC patients who underwent total thyroidectomy with radioactive iodine remnant ablation therapy. Pathologic grades of LT were separated at two points, chronic lymphocytic thyroiditis (CLT) and Hashimoto thyroiditis (HT). Patients were divided into two groupings according to the presence of the diseases (Grouping 1; patients with CLT or HT and without CLT or HT, Grouping 2; patients with HT and without HT). The groupings were compared according to recurrence, clinicopathologic and ultrasound (US) characteristics, and disease free survival. **Results:** Of 144 patients, 41 had CLT and 19 had HT. There were 10 patients (6.9%) with tumor recurrence. In both groupings, the presence of calcification was more frequently associated with patients with LT ( $p=0.041$  and  $0.047$ , respectively). In Grouping 2, the mean age at diagnosis was older in patients without HT compared to patients with HT ( $p=0.032$ ). On multivariate analysis, the presence of LT was not an independent predictor of recurrence in both groupings. For both groupings, pathologic tumor size and taller than wide shape on US were independent predictors of recurrence. The presence of LT in PTC patients did not affect recurrence. **Conclusion:** There was no relationship between PTC prognosis and different grades of LT. Pathologic tumor size and taller than wide shape on ultrasound were independent predictors of PTC recurrence regardless of concurrent LT.

**Key Words:** Lymphocytic thyroiditis, papillary thyroid carcinoma, pathological grade, ultrasonography, prognostic factor

## INTRODUCTION

Hashimoto thyroiditis (HT) is a common finding in resected thyroid specimens.<sup>1</sup> However, even though other aspects of HT have been extensively studied, there is still controversy on whether patients with papillary thyroid carcinoma (PTC) and concurrent HT are associated with favorable outcomes.<sup>2-10</sup> Whereas several reports concluded that better prognosis was shown in the patients with the two diseases at the same time,<sup>4,6,7,11</sup> the other reports conclude that HT was no significant prognos-

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tic factor predicting the outcome of PTC patients.<sup>2,3</sup>

Autoimmune thyroiditis, of which the pathologic hallmark is lymphocytic infiltration, can show a certain pathologic spectrum from lymphocytic infiltration only (chronic lymphocytic thyroiditis, CLT) to progressive loss of thyroid follicular cells, a concomitant replacement of the gland by lymphocytes, and the formation of germinal centers associated with fibrosis (HT).<sup>12</sup> As the disease progresses the cellular infiltrate and the fibroblastic tissue increase, resulting in the disorganization and destruction of thyroid tissue.<sup>13</sup> Therefore, this certain spectrum of pathologic features may affect the prognosis of PTC patients in different ways. To the best of our knowledge, no reports have compared CLT and HT with the prognosis of PTC. Therefore, our goal was to investigate the prognosis of PTC patients according to the presence of CLT or HT.

## MATERIALS AND METHODS

The Institutional Review Board of Severance Hospital approved this retrospective observational study and required neither patient approval nor informed consent for review of patients' images and medical records.

### Study population

Between April 2003 and December 2004, preoperative ultrasound (US) and pathologic slides were both found available for 356 PTC patients. 119 patients were excluded from this study as they had another coexisting primary site of cancer (n=15), previous surgical history of the thyroid gland (n=14), or follow up loss in 5 years (n=90). For the survival analysis, patients who underwent the same therapy had to be selected for the study. Therefore, among the remaining 237 patients who underwent both total thyroidectomy with radioactive iodine remnant ablation were selected, making a total of 144 patients for the study population.

### Ultrasonographic features

US images were obtained using 5–12-MHz linear transducers (HDI 5000 and IU-22, respectively; Philips, Bothell, WA, USA). All US examinations were reviewed on a GE Centricity PACS workstation (GE Healthcare, Milwaukee, WI, USA) by one radiologist (K.J.Y.). US features of thyroid cancers were described by composition, echogenicity, margin, calcification, and shape.<sup>14</sup> The internal composition was classified as solid and mixed. The echogenicity of a nodule was

categorized as iso- or hypoechogenicity (which was defined as iso- or hypoechogenic compared to the normal thyroid gland) and marked hypoechogenicity (which was defined as hypoechogenic compared to the strap muscle). The margin was categorized as well defined and not well defined. Calcification was categorized as presence of calcification and without calcification. The shape was described as wider than tall (which was defined as a ratio of the transverse diameter to the anteroposterior diameter of <1) and taller than wide (which was defined as a ratio of the transverse diameter to the anteroposterior diameter of  $\geq 1$ ).

### Histopathologic analysis

All surgical specimens of the 144 patients were re-evaluated by one pathologist (K.H.K.). Background thyroid pathology was evaluated based upon the presence of lymphocytic thyroiditis (LT). In this study, LT included both CLT and HT. CLT was defined with the histologic features of the presence of diffuse lymphocytic infiltrate, oxyphilic cells, and formation of lymphoid follicles with germinal centers. HT was defined with the histologic features of diffuse lymphocytic thyroiditis with follicular atrophy, diffuse destruction of thyroid follicles, fibrosis, and follicular cell regeneration.<sup>12</sup> Peritumoral inflammatory response was not considered as lymphocytic thyroiditis change.

### Postoperative management and follow-up

Patients were followed every six months in the first three years after surgery. Afterwards, follow-up evaluations took place every twelve months. Recurrence was defined with elevated serum Tg, uptake on <sup>131</sup>I whole body scan, or cytologic confirmation of PTC. US-guided fine needle aspiration (US-FNA) was performed to obtain cytopathologic specimens to confirm recurrence. Patients with no detectable Tg, no regional or distant metastasis on imaging studies, no evidence of regional recurrence on neck US, and benign cytology results after US-FNA were classified as the no recurrence group.

### Data and statistical analysis

In this study, LT was divided into CLT and HT for analysis. Two different groupings were formed by two different reference points (CLT and HT) of LT. For Grouping 1, subjects were divided into PTCs without LT (including both CLT and HT) and PTCs with LT. For Grouping 2, subjects were divided into PTCs without HT and PTCs with HT. We used the independent t-test for continuous variables and the chi-

square test for categorical variables to compare clinicopathologic characteristics among the two different groupings.

Disease free survivals were calculated by the Kaplan-Meier method and the log-rank sum test according to the presence of LT (including both CLT and HT) or HT. Univariate and multivariate Cox proportional hazard regression models were used to determine the association between clinicopathologic parameters and recurrence during the follow-up period in the two groupings. A two-tailed *p* value <0.05 was considered statistically significant. Statistical analysis was performed using SAS software (version 9.1.3; SAS Institute, Cary, NC, USA).

## RESULTS

Clinicopathologic characteristics of the included 144 patients are summarized in Table 1. The follow-up period ranged from 38 to 92 months (mean, 68.9±8.1 months). Of the 144 patients, 41 had CLT and 19 had HT. There were 10 patients (6.9%) with tumor recurrence. Among the 10 patients with recurrence, one had CLT and two had HT. Ta-

**Table 1. Clinicopathologic Characteristics in 144 Patients Who Underwent Total Thyroidectomy and with Radioactive Iodine Remnant Ablation**

Characteristics	Value
Total number	144
Age	
Age at diagnosis (yrs)	47.9±10.8 (25-75)
Groups (<45/≥45 yrs)	58/86
Gender	
Female, n (%)	133 (92.4)
Male, n (%)	11 (7.6)
Primary tumor	
Pathologic size (mm)	9.2±6.4 (2-40)
Multifocality, n (%)	39 (27.1)
Extrathyroidal extension, n (%)	35 (24.3)
Nodal involvement	
Central compartment, n (%)	61 (42.4)
Lateral compartment, n (%)	7 (4.9)
Recurrence (%)	10 (6.9)
Lateral lymph node	6
Biochemical	3
Operation bed	1
Contralateral thyroid gland	1

n, number.

**Table 2. Difference in Clinicopathologic and Ultrasound Characteristics between PTC Patients with or without CLT or HT**

	Without LT (n=103)	With LT (n=41)	<i>p</i> value	Without HT (n=125)	With HT (n=19)	<i>p</i> value
Male gender	11 (10.7)	0 (0.0)	0.034	11 (8.8)	0 (0.0)	0.360
Mean age at diagnosis (yrs)	48.9 (25-75, 10.8)	45.4 (28-69, 10.4)	0.078	48.6 (25-75, 10.7)	43.0 (28-65, 10.4)	0.032
Mean tumor size (mm)	9.1 (2-40, 6.4)	9.3 (3-35, 6.6)	0.838	9.3 (2-40, 6.7)	8.6 (3-15, 3.8)	0.698
Multiplicity (n=39)	28 (27.2)	11 (26.8)	1.000	32 (25.6)	7 (36.8)	0.405
Central LN metastasis (n=61)	39 (37.9)	22 (53.7)	0.095	50 (40.0)	11 (57.9)	0.212
Lateral LN metastasis (n=7)	5 (4.9)	2 (4.9)	1.000	6 (4.8)	1 (5.3)	1.000
Extrathyroidal extension (n=35)	24 (23.3)	11 (26.8)	0.671	31 (24.8)	4 (21.1)	1.000
Recurrence (n=31)	25 (24.3)	26 (63.4)	0.264	28 (22.4)	3 (15.8)	0.765
US features						
Composition			0.675			1.000
Solid (n=138)	98 (95.1)	40 (97.6)		119 (95.2)	19 (100.0)	
Mixed (n=6)	5 (4.9)	1 (2.4)		6 (4.8)	0 (0.0)	
Echogenicity			1.000			0.528
Iso & hypoechogenicity (n=117)	84 (81.6)	33 (80.5)		100 (80.0)	17 (89.5)	
Marked hypoechogenicity (n=27)	19 (18.4)	8 (19.5)		25 (20.0)	2 (10.5)	
Margin			0.487			1.000
Well defined margin (n=27)	21 (20.4)	6 (14.6)		24 (19.2)	3 (15.8)	
Not well defined margin (n=117)	82 (79.6)	35 (85.4)		101 (80.8)	16 (84.2)	
Calcifications			0.041			0.047
Presence of calcifications (n=82)	53 (51.5)	29 (70.7)		67 (53.6)	15 (78.9)	
No calcification (n=62)	50 (48.5)	12 (29.3)		58 (46.4)	4 (21.1)	
Shape			0.185			0.800
Taller than wide (n=90)	68 (66.0)	22 (53.7)		79 (63.2)	11 (57.9)	
Wider than tall (n=54)	35 (34.0)	19 (46.3)		46 (36.8)	8 (42.1)	

PTC, papillary thyroid carcinoma; CLT, chronic lymphocytic thyroiditis; HT, Hashimoto thyroiditis; LT, lymphocytic thyroiditis; LN, lymph node; US, ultrasound.

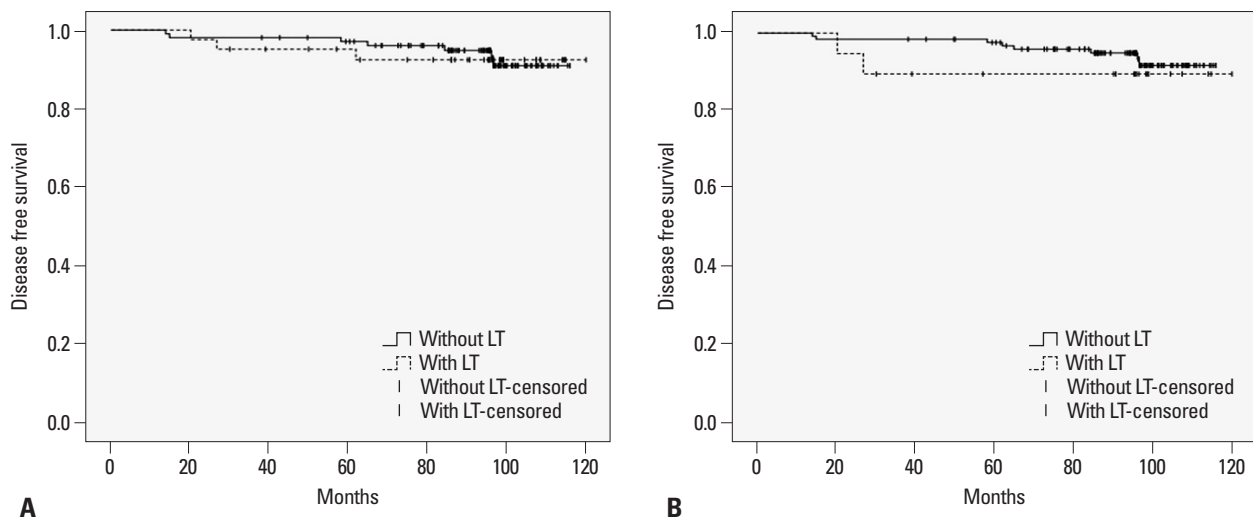
ble 2 shows the clinicopathologic and US characteristics of the two groupings. CLT or HT was only found in patients of the female gender. In Grouping 2, the mean age at diagnosis was older in patients without HT ( $p=0.032$ ). In both groupings, the presence of calcification was more frequently associated with patients with LT (including both CLT and HT) or HT ( $p=0.041$  and  $0.047$ , respectively).

The Kaplan-Meier analysis demonstrated that the presence of LT (both CLT and HT) or HT in PTC patients did not alter the probability of recurrence developing (Fig. 1). To identify predictive factors of recurrence, a Cox proportional hazard model was created. Univariate and multivariate analysis results are listed in Table 3 and 4. On multivariate analysis, nei-

ther LT nor HT was an independent predictor of recurrence. Pathologic tumor size and taller than wide shape on US were independent predictors of recurrence in both groupings.

## DISCUSSION

Lymphocytic thyroiditis has a certain pathologic spectrum with various degrees of inflammatory change with lymphocytic infiltration.<sup>15</sup> Although a number of investigators have classified LT into several types according to different degrees of lymphocytic infiltration, epithelial changes, and fibrosis (Table 5),<sup>15-21</sup> most pathologists have used CLT and



**Fig. 1.** Disease free survivals in patients with or without lymphocytic thyroiditis (LT, including both chronic lymphocytic thyroiditis and Hashimoto thyroiditis) (A) and Hashimoto thyroiditis (HT) (B). Log-rank test  $p$ -value of A and B is 0.880 and 0.459, respectively.

**Table 3.** Univariate and Multivariate Predictors of Recurrence When LT Including Both CLT and HT Is Considered as One of the Clinicopathologic Parameters

Clinicopathologic parameter	Univariate analysis		Multivariate analysis	
	Hazard ratio (95% CI)	$p$ value	Hazard ratio (95% CI)	$p$ value
Male gender	1.264 (0.160, 9.977)	0.824	2.887 (0.270, 30.848)	0.390
Mean age at diagnosis	0.986 (0.930, 1.046)	0.639	0.962 (0.899, 1.029)	0.257
Mean tumor size (mm)	1.085 (1.030, 1.143)	0.002	1.251 (1.075, 1.454)	0.004
Multiplicity	1.856 (0.524, 6.579)	0.338	2.424 (0.479, 12.261)	0.284
Central LN metastasis	1.784 (0.501, 6.347)	0.372	1.322 (0.286, 6.118)	0.721
Lateral LN metastasis	2.760 (0.344, 22.144)	0.340	5.992 (0.165, 217.500)	0.329
Extrathyroidal extension	3.040 (0.878, 10.520)	0.079	1.776 (0.426, 7.414)	0.431
LT including CLT and HT	1.110 (0.287, 4.295)	0.880	1.145 (0.242, 5.411)	0.865
US features				
Solid composition	0.415 (0.052, 3.278)	0.404	65.041 (0.351, 12049.760)	0.117
Hypoechoogenicity	NA		NA	
Not well defined margin	2.089 (0.265, 16.489)	0.485	3.229 (0.093, 112.626)	0.518
Presence of calcifications	3.030 (0.643, 14.269)	0.161	1.642 (0.295, 9.145)	0.572
Taller than wide shape	1.499 (0.387, 5.809)	0.558	10.013 (1.133, 88.484)	0.038

LT, lymphocytic thyroiditis; CLT, chronic lymphocytic thyroiditis; HT, Hashimoto thyroiditis; CI, confidence interval; LN, lymph node; US, ultrasound; NA, not applicable.

**Table 4.** Univariate and Multivariate Predictors of Recurrence When HT Is Considered as One of the Clinicopathologic Parameters

Clinicopathologic parameter	Univariate analysis		Multivariate analysis	
	Hazard ratio (95% CI)	<i>p</i> value	Hazard ratio (95% CI)	<i>p</i> value
Male gender	1.264 (0.160, 9.977)	0.824	2.795 (0.280, 27.929)	0.382
Mean age at diagnosis	0.986 (0.930, 1.046)	0.639	0.963 (0.899, 1.031)	0.276
Mean tumor size (mm)	1.085 (1.030, 1.143)	0.002	1.249 (1.075, 1.451)	0.004
Multiplicity	1.856 (0.524, 6.579)	0.338	2.374 (0.479, 11.765)	0.290
Central LN metastasis	1.784 (0.501, 6.347)	0.372	1.316 (0.278, 6.232)	0.729
Lateral LN metastasis	2.760 (0.344, 22.144)	0.340	6.019 (0.168, 215.656)	0.326
Extrathyroidal extension	3.040 (0.878, 10.520)	0.079	1.801 (0.435, 7.458)	0.417
Hashimoto thyroiditis	1.783 (0.378, 8.407)	0.465	1.14 (0.187, 6.948)	0.887
US features				
Solid composition	0.415 (0.052, 3.278)	0.404	65.607 (0.358, 12025.990)	0.116
Hypoechoogenicity	NA		NA	
Not well defined margin	2.089 (0.265, 16.489)	0.485	3.283 (0.096, 112.225)	0.510
Presence of calcifications	3.030 (0.643, 14.269)	0.161	1.656 (0.299, 9.160)	0.563
Taller than wide shape	1.499 (0.387, 5.809)	0.558	9.564 (1.036, 88.266)	0.046

HT, Hashimoto thyroiditis; CI, confidence interval; LN, lymph node; US, ultrasound; NA, not applicable.

**Table 5.** Gradings of Lymphocytic Thyroiditis Proposed by Previous Literatures

Author	Cytological groups			
	Grade	Lymphocytic infiltration	Epithelial change (Hurthle cell metaplasia)	Fibrosis
LiVolsi <sup>15</sup>	Focal	Mild to moderate	Unusual	Unusual
	Mixed	Moderate	Normal to hyperplasia to metaplasia	Minimal
	Oxyphilic	Diffuse	Diffuse	Diffuse
Bhatia, et al. <sup>16</sup>	0	No	NA	NA
	1	Few	NA	NA
	2	Moderate	NA	NA
	3	Germinal center formation	NA	NA
Kebebew, et al. <sup>17</sup>	0	No	NA	NA
	1	Scanty	NA	NA
	2	Focally dense	NA	NA
	3	Diffuse dense	NA	NA
Kumar, et al. <sup>18</sup>	1	Minimal	NA	NA
	2	Moderate to heavy	NA	NA

NA, not applicable.

HT. CLT is defined when histologic characteristics meet the following conditions; presence of diffuse lymphocytic infiltrate, oxyphilic cells, and the formation of lymphoid follicles or reactive germinal centers.<sup>8</sup> HT has been differentiated from CLT and is defined when histologic characteristics meet the following additional conditions along with the characteristics of CLT; presence of Hurthle cells and varying degree of acini atrophy.<sup>22</sup>

The nature association between LT and PTC is still uncertain. A molecular study concluded that multiple occult tumors exist in HT at high frequency.<sup>23</sup> Some studies suggested that chronic thyroiditis will induce malignant transformation by enhancing mitosis and proliferation of thyroid

cells.<sup>24</sup> Although its nature remains uncertain, studies regarding the relationship between CLT or HT and PTC have been reported. As HT patients showed a higher incidence of thyroid carcinoma, HT was thought to be a predisposing factor in the development of thyroid carcinoma.<sup>25</sup> However, there was a report showing that the pathogenesis of PTC itself stimulates lymphocytic infiltration and the autoimmune mechanism was suggested as a result of malignant pathogenesis rather than as a premalignant factor.<sup>26</sup> In fact, CLT and HT have been reported to be favorable factors in the prognosis of PTC,<sup>4,7,17,27</sup> although the issue remains somewhat controversial.<sup>2,3</sup> The presence of CLT or HT in PTC patients has been related to lower T stage, less extrathyroi-

dal extension, or less nodal metastasis compared to patients without CLT.<sup>4,7,17,27</sup> Furthermore, disease free survival was found to be significantly longer in PTC patients with coexisting CLT.<sup>8</sup> On the other hand, other studies have shown CLT or HT not affecting any prognostic features such as size, angioinvasion, or multifocality, thereby showing no association between the presence of CLT or HT and PTC aggressiveness.<sup>2,3</sup> Although many investigators evaluated the relationship between CLT or HT and the prognostic outcomes of PTC patients, they mixed “CLT” with “HT” and in some cases, even categorized them as the same pathologic condition. Also, to our knowledge, there have been no published reports on the relationship between different pathologic grades of LT and the prognostic outcomes of PTC. Therefore, we sought to investigate whether the pathologic grade of LT can affect the outcome of PTC patients along with other clinicopathologic and US features.

Factors influencing a poor outcome of thyroid tumor recurrence include older age, male gender, larger size, cervical node or distant metastasis, extrathyroidal extension, multiplicity of the tumor, and tumor stage.<sup>5,28</sup> In our study, larger PTC is significantly associated with a higher recurrence rate of PTC regardless of the presence of CLT or HT, similar to previous reports that show larger PTC nodules having an association with poor prognostic factors.<sup>5,29</sup> There have been several reports about the relationship of US characteristics with clinical outcomes. Patients with PTC with benign looking results on US had better prognosis than ones with malignant looking results on US.<sup>30</sup> Ill-defined margins or the presence of calcification was associated with lymph node metastasis in PTC patients.<sup>31,32</sup> PTCs with taller-than-wide shape on US were associated with extrathyroidal extension and BRAF mutation which may be a poor prognostic factor.<sup>33</sup> Our study shows that a PTC patient with taller-than-wide shape on US is more likely to recur with or without LT. Further studies will be needed to verify this.

There are some limitations to our study. First, this is a retrospective study and has selection bias as we excluded patients with other primary malignancies, with previous history of surgery or other procedures at the thyroid gland, or with a follow-up of less than 5 years. Second, all US image analyses were based on the retrospective review of previously taken images. The interpretation of US findings by the reviewer could have been different from the actual US performer. Third, only one pathologist and radiologist reviewed the specimens and US findings. Therefore, interobserver variability should be considered in future studies. Fourth,

there was a relatively small number of the study population to compare disease free survival between each group of patients. Further study is needed with larger number of patients in each group to obtain more profound results.

We conclude that there was no relationship between PTC prognosis and different grades of LT. Pathologic tumor size and taller than wide shape on US were independent predictors of PTC recurrence regardless of concurrent LT.

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