

# Identifying risk factors of lateral lymph node recurrence in clinically node-negative papillary thyroid cancer

Young Jae Ryu, MD, Shin Jae Kang, MD, Jin Seong Cho, MD, Jung Han Yoon, MD, PhD, Min Ho Park, MD, PhD\*

## Abstract

There is still debate regarding the role of routine central lymph node (LN) dissection in treating clinically node-negative papillary thyroid cancer (PTC). The aim of this study was to investigate the risk factors for lateral recurrence after total thyroidectomy and prophylactic bilateral central LN dissection in clinically node-negative PTC patients.

We retrospectively collected the medical records of 1406 PTC patients who underwent total thyroidectomy and prophylactic bilateral central LN dissection between January 2004 and December 2008. We used Cox- proportional hazards regression analyses to inspect the predictive factors for recurrence.

During a median follow-up of 107 months (range, 13–164 months), 68 (4.8%) and 37 (2.6%) patients experienced recurrence in any lesion and in lateral neck LN, respectively. Male, main tumor size > 1 cm, nodal factors (pathologic N1a, positive delphian LN, and LN ratio >0.15), lymphovascular invasion, and extrathyroidal extension (ETE) were significantly associated with lateral neck LN recurrence in univariate analysis. Multivariate analysis showed that male (hazard ratio [HR], 2.217; 95% confidence interval [CI], 1.057–4.647;  $P = .035$ ), main tumor size > 1 cm (HR, 2.257; 95% CI, 1.138–4.476;  $P = .020$ ), pathologic N1a (HR, 5.957; 95% CI, 2.573–13.789;  $P < .002$ ), minor ETE (vs no ETE; HR, 3.027; 95% CI, 1.315–6.966;  $P = .009$ ), and gross ETE (vs no ETE; HR, 4.058; 95% CI, 1.685–9.774;  $P = .002$ ) were independent predictors for lateral neck LN recurrence.

Among patients with pathologic N1a, those with LN ratio of more than 0.55 had worse lateral neck LN recurrence-free survival. Lateral neck LN recurrence in clinically node-negative PTC patients is predicted by the factors of male, main tumor size > 1 cm, ETE, and pathologic N1a.

**Abbreviations:** AJCC = American Joint Committee on Cancer, CI = confidence interval, CLT = chronic lymphocytic thyroiditis, CT = computed tomography, ENE = extranodal extension, ETE = extrathyroidal extension, HR = hazard ratio, LN = lymph node, LVI = lymphovascular invasion, PTC = papillary thyroid cancer, RFS = recurrence-free survival, ROC = receiver operating characteristic, Tg = thyroglobulin, TSH = thyroid stimulating hormone, US = ultrasonography.

**Keywords:** papillary thyroid cancer, prophylactic central neck dissection, recurrence

## 1. Introduction

Papillary thyroid cancer (PTC) is the most common histologic type of thyroid cancer, accounting for 80% to 85% of thyroid malignancies.<sup>[1]</sup> The incidence of PTC has been increasing for decades worldwide. The prognosis for PTC is better than that for other thyroid malignancies, with a 10-year survival rate over 95% and 93% survival after 20 years.<sup>[2]</sup> By the characteristic of lymphogenous spread from the thyroid, lymph node (LN)

involvement is commonly observed in up to 80% of PTC patients.<sup>[3]</sup> Although positive regional LN is associated with higher regional recurrence rate, it is of little importance for mortality. There is a consensus that therapeutic central LN dissection should be performed for clinically node-positive PTC in the central compartment; however, it is still debatable whether or not to perform prophylactic central LN dissection in clinically node-negative PTC patients. Prophylactic central LN dissection enables accurately reflecting nodal stage and contributes to decision-making regarding postoperative radioactive iodine therapy and thyroid-stimulating hormone suppression during follow-up. Additionally, prophylactic central LN dissection is helpful for decreasing disease-specific recurrence, maintaining undetectable thyroglobulin (Tg) during postoperative follow-up, and avoiding complications from re-operating in the central compartment. However, prophylactic central LN dissection is considered an overtreatment for pathologic node-negative patients with less-aggressive PTC.

The number of patients with clinically central node-negative PTC has been increasing for decades because of the sensitivity of cancer detection with ultrasonography (US) and advantage of molecular markers.<sup>[4,5]</sup> However, the possibility of detecting suspicious central LN is lower than that of detecting lateral neck LN.<sup>[5]</sup> Due to high rates of LN metastasis and relatively low sensitivity of imaging modalities in the central neck

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Department of Surgery, Chonnam National University Medical School, 322 Seoyang-ro Hwasun-eup, Hwasun-gun Jeonnam, Gwangju, South Korea.

\* Correspondence: Min Ho Park, Department of Surgery, Chonnam National University Medical School, 322 Seoyang-ro Hwasun-eup, Hwasun-gun Jeonnam, Gwangju, 58128, South Korea (e-mail: mhpark@chonnam.ac.kr).

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compartment, prophylactic central LN dissection is considered a serious surgical strategy to resolve subclinical central LN metastases.

LN metastasis in PTC follows a stepwise spread pattern. It spreads to the lateral neck compartment from the central neck compartment. However, in patients who have undergone central and lateral neck LN dissection, skip metastasis (lateral neck LN metastases without central LN metastasis) is not a rare event.<sup>[6]</sup> Predictors of recurrence in the lateral neck compartment for PTC patients without lateral neck LN metastases at first surgery are currently unknown. Hence, the aim of this study was to investigate the risk factors for recurrence in lateral neck LN after total thyroidectomy and bilateral central neck dissection in clinically node-negative PTC patients.

## 2. Methods

### 2.1. Patients

We reviewed the medical records of 3279 patients who underwent thyroid surgery between January 2004 and December 2008 at Chonnam National University Hwasun Hospital. Exclusion criteria were as follows: patients who had history of thyroid lobectomy due to thyroid malignancy or benign disease, who underwent completion thyroidectomy due to recurrence of any histologic type, who underwent total thyroidectomy because of other than PTC, who underwent lateral neck LN dissection, who had clinically node-positive PTC in the central compartment, who had distant metastases at initial diagnosis, who had secondary malignancy during follow-up, who had abnormal thyroid function test results before surgery, who had history of neck surgery or radiation therapy due to other disease, who did not undergo central neck dissection, or who had less than 1 year of follow-up. All patients were administered physical examination, neck US, and neck computed-tomography (CT) before surgery. Images were carefully reviewed to check suspicious LN in all patients' central compartments. A total of 1406 PTC patients who underwent total thyroidectomy and prophylactic central LN dissection were enrolled in this study. This retrospective study was approved by the Institutional Review Board in our hospital.

Patients' age, gender, main tumor size, multifocality and bilaterality of tumor, number of harvested and metastatic LNs, LN ratio (number of metastatic LNs divided by number of harvested LNs), chronic lymphocytic thyroiditis, T stage, extrathyroidal extension (ETE), lymphovascular invasion, complications, and recurrence were thoroughly reviewed. Cancer staging followed the American Joint Committee on Cancer (AJCC) recommendations.<sup>[7]</sup> T stage and ETE were reclassified according to recent AJCC recommendations.<sup>[8]</sup>

### 2.2. Operation and postoperative follow-up

All patients underwent total thyroidectomy and comprehensive central LN dissection in level VI (prelaryngeal, pretracheal, paratracheal, and and/or paraesophageal node) and level VII (upper mediastinal node). Based on tumor and node characteristics, some patients received 30 to 150 mCi of radioactive iodine therapy at 2 to 3 months after surgery. All patients were followed up every 3 to 6 months for 3 years and annually thereafter. All patients also received regular physical examinations, neck US, chest radiography, whole-body iodine scanning, and measurement of serum-free thyroxine and thyrotropin, Tg, and anti-Tg

antibody concentrations. Lesions of suspicious recurrence were evaluated with fine-needle aspiration cytology if they were accessible. Recurrence was defined as structural recurrence confirmed by using image modalities, such as neck US, neck CT, 18F-fluorodeoxyglucose positron emission tomography CT, whole body scan, and histologic examinations. Most patients with structural recurrence underwent reoperation; however, if the lesion of recurrence was unresectable or in a distant organ, radioactive iodine therapy was considered rather than operation.

### 2.3. Complications

Permanent hypoparathyroidism was defined as below-normal postoperative serum parathyroid hormone with concomitant low calcium that required more than 6 months of calcium and vitamin D supplementation. Hypoparathyroidism that resolved within 6 months was considered as transient. Recurrent laryngeal nerve injury was classified as transient or permanent based on 6-month postoperative findings. Bleeding was defined as symptoms or signs of bleeding for cases of conservative treatment or reoperation.

### 2.4. Statistical analysis

The primary end point was recurrence in the lateral neck compartment. We defined any lesion and lateral neck nodal recurrence-free survival (RFS) as the time between the first operation and detection of recurrence in any lesion and in the lateral neck compartment respectively. Continuous variables are presented as median (range) while categorical variables are presented as number (percent). A univariate Cox proportional hazards model was used to analyze relationships between the clinicopathologic variables and RFS. We also performed multivariate Cox proportional hazards regression analyses by way of backward elimination using the variables with  $P < .05$  in the univariate analyses. Receiver operating characteristic (ROC) curve was used to calculate an optimal LN ratio cutoff, and log-rank test and Kaplan–Meier curve were used to calculate differences in RFS. All statistical analyses were performed using SPSS version 23.0 (IBM Inc., Armonk, NY, USA). Statistical significance was considered when  $P$  value was less than .05.

## 3. Results

### 3.1. Patients' demographics

Of 1406 patients, 190 (13.5%) were males. Median (range) age of all patients was 47 years (15–79). A total of 358 (25.5%) patients were over 55 years. Four hundred thirty-one (30.7%) patients had main tumors of more than 1 cm in size while 145 (10.3%) had tumors of more than 2 cm in total size. Most patients (1231, 87.6%) had tumors limited to the thyroid (T1, T2, T3a). One hundred seventeen (8.3%) patients had tumors with gross ETE invading only strap muscles while 58 (4.1%) had stage T4a tumors. Three hundred twenty-four (23.0%) and 294 (20.9%) patients had tumor multifocality and bilaterality, respectively. Four hundred sixty-four (33.0%) patients had more than 6 harvested LNs. Four hundred sixty-seven (33.2%) showed pathologic N1a while 50 (3.6%) showed positive delphian LN. Chronic lymphocytic thyroiditis (CLT) was observed in 578 (41.1%) patients, and 27 (1.9%) patients presented lymphovascular invasion (LVI). Five eighty-nine (41.9%) patients underwent postoperative radioactive iodine therapy. Of a total of 1406

**Table 1**  
**Patients' demographics.**

Variables	All patients number (%)	All recurrence number (%)	Lateral recurrence number (%)
Total	1,406	68	37
Age, median (range)	47 (15–79)	46 (15–75)	46 (15–75)
≥55 years	358 (25.5)	13 (19.1)	6 (16.2)
Male	190 (13.5)	15 (22.1)	10 (27.0)
BMI ≥25 kg/m <sup>2</sup>	520 (37.0)	21 (30.9)	13 (35.1)
Diabetes/hypertension	79 (5.6)/ 219 (15.6)	9 (13.2)/ 9 (13.2)	4 (10.8)/ 5 (13.5)
Preoperative TSH			
<2 mU/L	829 (59.0)	45 (66.2)	24 (64.9)
≥2 mU/L	577 (41.0)	23 (33.8)	13 (35.1)
Main tumor size >1 cm	431 (30.7)	41 (60.3)	23 (62.2)
Total tumor size >2 cm	145 (10.3)	18 (26.5)	12 (32.4)
T stage			
T1a/T1b	900 (64.0)/ 278 (19.8)	22 (32.4)/ 23 (33.8)	11 (29.7)/ 9 (24.3)
T2	50 (3.6)	4 (5.9)	4 (10.8)
T3a/T3b	3 (0.2)/ 117 (8.3)	0/ 8 (11.8)	0/ 5 (13.5)
T4a	58 (4.1)	11 (16.2)	8 (21.6)
Multifocality	324 (23.0)	24 (35.3)	12 (32.4)
Bilaterality	294 (20.9)	20 (29.4)	10 (27.0)
Nodal factor			
Harvested lymph node ≥6	464 (33.0)	23 (33.8)	16 (43.2)
Pathologic N1a	467 (33.2)	52 (76.5)	30 (81.1)
Positive delphian node	50 (3.6)	9 (13.2)	6 (16.2)
Chronic lymphocytic thyroiditis	578 (41.1)	26 (38.2)	13 (35.1)
Lymphovascular invasion	27 (1.9)	3 (4.4)	3 (8.1)
Radioactive iodine therapy	589 (41.9)	53 (77.9)	31 (83.8)
Recurrence	68 (4.8)		37 (100)
Central recurrence	37 (2.6)	37 (54.4)	8 (21.6)
Lateral recurrence	37 (2.6)	37 (54.4)	37 (100)
Distant metastasis	3 (0.2)	3 (4.4)	1 (2.7)
Median follow up	107 months (13–164)		

BMI=body mass index, TSH=thyroid stimulating hormone.

patients, recurrence occurred in 68 (4.8%). Of these, 37 (2.6%), 37 (2.6%), 3 (0.2%) had recurrence in the operative bed or the central neck compartment, recurrence in the lateral neck compartment, and in distant lesions, respectively. Of 37 patients with recurrence in the lateral neck compartment, 8 (21.6%) recurrences were found in the central neck compartment, and including 1 (2.7%) recurrence in the lung simultaneously. Median follow-up (range) was 107 (13–164) months (Table 1).

### 3.2. Univariate analyses according to recurrence in any lesion and in the lateral compartment

Univariate analysis using Cox-proportional hazards regression model for all patients showed that male gender, main tumor size of more than 1 cm, multifocality, nodal factors (pathologic N1a, positive delphian LN, LN ratio of more than 0.15), and ETE were significantly associated with recurrence in any lesion while age, BMI, bilaterality of tumors, number of harvested LNs, LVI, or CLT showed no significant association with recurrence (Table 2). Of patients with or without recurrence in the lateral neck compartment, univariate analyses indicated that male gender, main tumor size of more than 1 cm, nodal factors (pathologic N1a, positive delphian LN, LN ratio of more than 0.15), LVI, and ETE had statistically significant correlations with recurrence. There were no statistically significant associations with age, BMI, multifocality and bilaterality of tumors, number of harvested LNs, or CLT (Table 2).

### 3.3. Multivariate analyses according to recurrence in any lesion and in the lateral compartment

Multivariate Cox-proportional hazards regression analyses showed that main tumor size of more than 1 cm (hazards ratio [HR], 2.255; 95% confidence interval [CI], 1.365–3.726;  $P=.001$ ), pathologic N1a (HR, 5.059; 95% CI, 2.853–8.970;  $P<.001$ ), minor ETE (vs no ETE, HR, 2.321; 95% CI, 1.315–4.097;  $P=.004$ ), and gross ETE (vs no ETE, HR, 2.331; 95% CI, 1.234–4.403;  $P=.009$ ) were significant predictors of recurrence in any lesion (Table 3). Male gender (HR, 2.217; 95% CI, 1.057–4.647,  $P=.035$ ), main tumor size more than 1 cm (HR, 2.257; 95% CI, 1.138–4.476;  $P=.020$ ), pathologic N1a (HR, 5.957; 95% CI 2.573–13.789;  $P<.001$ ), minor ETE (vs no ETE, HR, 3.027; 95% CI, 1.315–6.966;  $P=.009$ ), and gross ETE (vs no ETE, HR, 4.058; 95% CI, 1.685–9.774;  $P=.002$ ) were independent risk factors for recurrence in the lateral neck compartment (Table 3).

### 3.4. Survival curve according to positive LN, LN ratio, and ETE

Patients with pathologic N1a had worse RFS than those with pathologic N0 irrespective of recurrence site (Fig. 1 A and B). Among patients with pathologic N1a, the LN ratio of 0.55 had 78.8% sensitivity and 57.1% specificity in ROC curve (area under the curve, 0.688;  $P<.001$ ). Patients with LN ratio of more

**Table 2****Univariate analyses according to recurrence.**

Variables	All patients, n=1,406			Patients with or without lateral recurrence, n=1,375		
	HR	95% CI	P	HR	95% CI	P
Age, more than 55 years	0.690	0.380–1.270	.234	0.566	0.236–1.358	.203
Male	1.908	1.075–3.384	.027	2.504	1.212–5.174	.013
BMI $\geq$ 25	0.775	0.463–1.296	.331	0.934	0.476–1.835	.844
Preoperative TSH						
<2 mU/L	1			1		
$\geq$ 2 mU/L	0.723	0.437–1.194	.205	0.766	0.390–1.505	.440
Main tumor size >1 cm	3.543	2.180–5.759	<.001	3.885	1.999–7.551	<.001
Total tumor size >2 cm	3.287	1.918–5.633	<.001	4.419	2.220–8.796	<.001
Multifocality	1.827	1.111–3.004	.018	1.617	0.813–3.220	.171
Bilaterality	1.597	0.948–2.690	.079	1.425	0.690–2.943	.339
Nodal factor						
More than 6 harvested LN	1.420	0.859–2.347	.171	1.886	0.979–3.636	.058
Pathologic N1a	6.840	3.905–11.979	<.001	9.170	4.028–20.880	<.001
Positive delphian node	4.516	2.239–9.107	<.001	5.803	2.421–13.911	<.001
LN ratio of more than 0.15	6.963	1.063–11.935	<.001	9.246	4.226–20.226	<.001
Lymphovascular invasion	2.480	0.779–7.892	.124	4.685	1.439–15.255	.010
Extrathyroidal extension	3.625	2.181–6.025	<.001	5.444	2.569–11.537	<.001
ETE						
No ETE	1			1		
Minor ETE	3.186	1.815–5.595	<.001	4.371	1.913–9.989	<.001
Gross ETE	4.507	2.439–8.326	<.001	7.593	3.246–17.764	<.001
CLT	0.874	0.536–1.426	.590	0.764	0.389–1.501	.435

BMI=body mass index, CI=confidence interval, CLT=chronic lymphocytic thyroiditis, ETE=extrathyroidal extension, HR=hazards ratio, LN=lymph node, TSH=thyroid stimulating hormone.

than 0.55 had worse RFS for any lesion and lesion in the lateral neck compartment (Fig. 2 A and B). Patients without ETE had more favorable RFS than those with minor ETE or gross ETE (Fig. 3 A and B).

### 3.5. Complications: all patients

Of a total of 1406 PTC patients, incidence rates of transient and permanent hypoparathyroidism were 6.1% (86 patients) and 1.9% (27 patients), respectively. Transient and permanent recurrent laryngeal nerve palsy were observed in 89 (6.3%) and 7 (0.5%) patients respectively. Seven patients showed postoperative bleeding. Two of these patients underwent

operative treatment while 5 recovered after conservative treatment (Tables 4 and 5).

## 4. Discussion

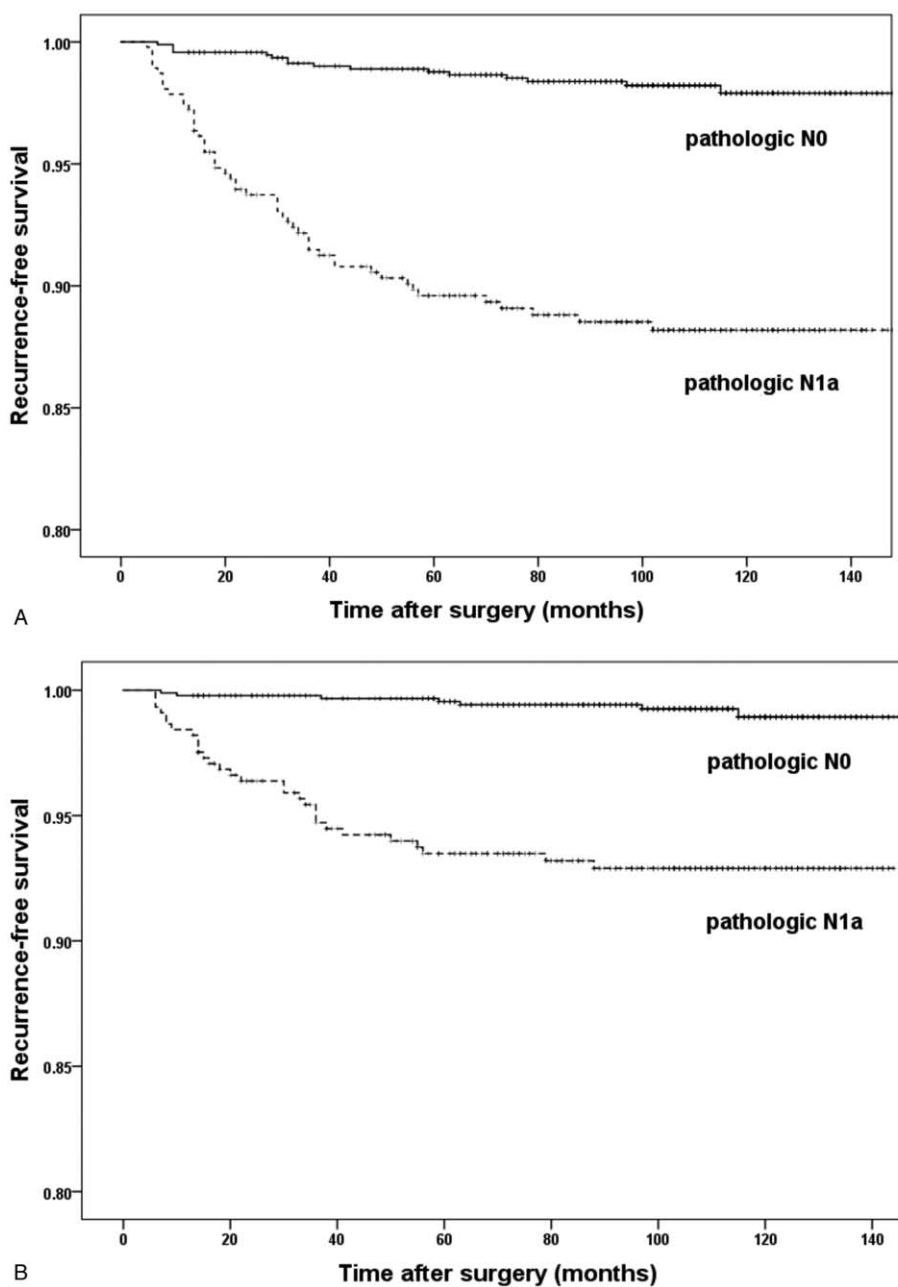
With this study, we aimed to identify predictors of recurrence in the lateral neck compartment in patients with clinically node-negative PTC. Of a total of 1406 patients, recurrence occurred in 37 (2.6%) patients in the lateral neck LN, lower than the previous findings from other studies (3–6.0%, 4–4.5%).<sup>[9,10]</sup> During a long follow-up period of 107 months (range, 13–164 months), recurrence in lateral neck LN was predicted by male, main tumor size of more than 1 cm, ETE, and nodal factors (pathologic N1a, positive delphian node, LN ratio >15%).

LN metastasis in PTC is common and lymphatic spread pattern originating from the thyroid is comparatively consistent. The general pattern first involves the central compartment and then ipsilateral lateral and contralateral lateral neck. A number of studies have reported that central LN metastasis is a prognostic factor for recurrence in the central compartment in patients who have undergone thyroidectomy and prophylactic central LN dissection.<sup>[11,12]</sup> Hartl et al have compared patients who underwent total thyroidectomy with and without prophylactic central LN dissection in clinically node-negative PTC and found that prophylactic central LN dissection has a significantly lower rate of 5-year retreatment (6.5% vs 14.7%,  $P=.01$ ).<sup>[13]</sup> Central LN metastasis at diagnosis is important for impact on loco-regional recurrence and an independent predictor of recurrence in the lateral neck compartment of PTC patients without cN1b.<sup>[10]</sup> When clinicians evaluate central LNs with preoperative imaging modalities, neck US and neck CT can reduce the number of subclinical central LN metastases and enable access for therapeutic central LN dissection. In some studies, the sensitivity of preoperative neck US plus neck CT is higher than that of neck

**Table 3****Multivariate analyses of all patients according to recurrence.**

	HR	95% CI	P
Sex			
Female	1		
Male	1.639	0.918–2.928	.095
Multifocality			
No	1		
Yes	1.412	0.851–2.342	.182
Tumor size			
$\leq$ 1 cm	1		
>1 cm	2.255	1.365–3.726	.001
Pathologic N			
N0	1		
N1a	5.059	2.853–8.970	<.001
ETE			
No ETE	1		
Minor ETE	2.321	1.315–4.097	.004
Gross ETE	2.331	1.234–4.403	.009

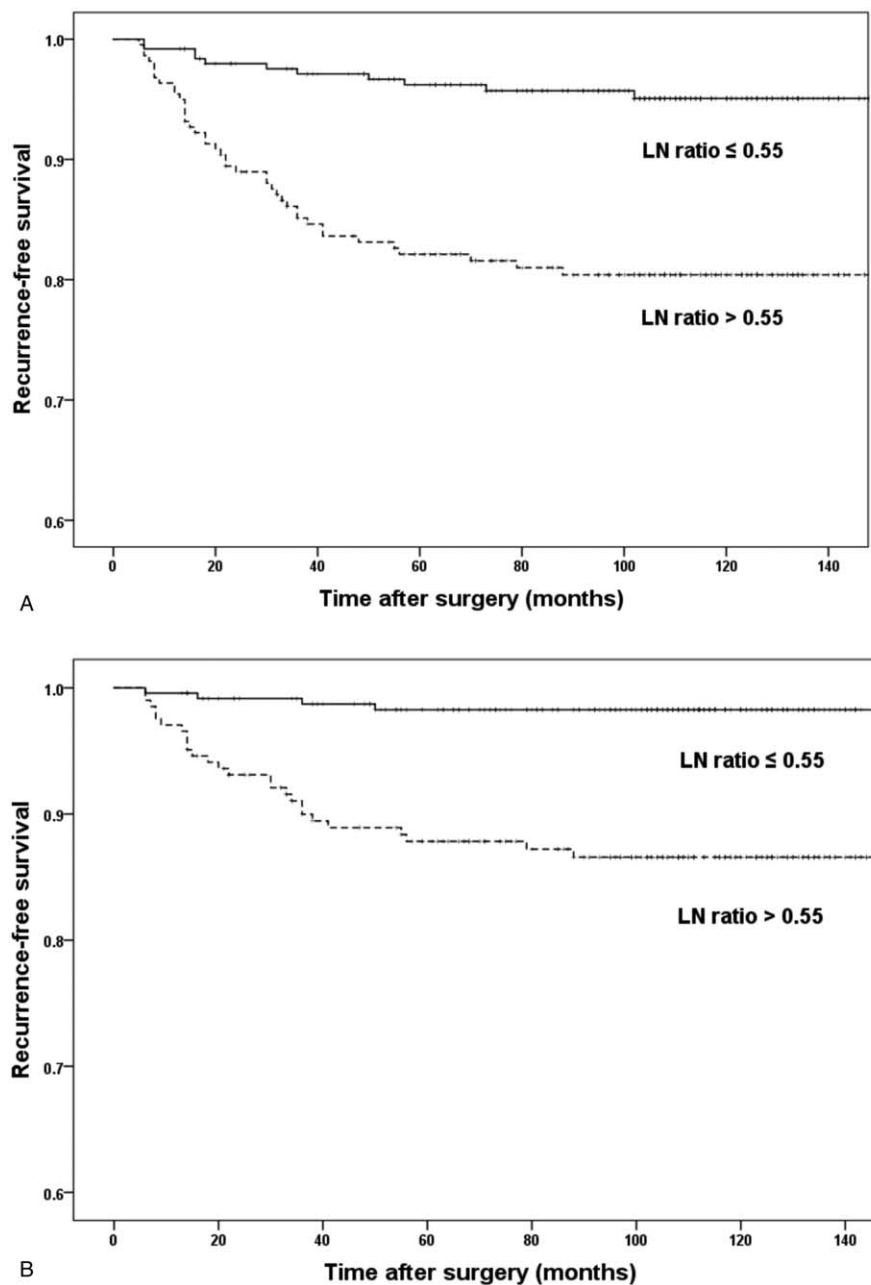
CI=confidence interval, ETE=extrathyroidal extension, HR=hazard ratio.



**Figure 1.** Recurrence-free survival curve according to pathologic N stage, (A) all patients, (B) patients with or without recurrence in the lateral neck compartment ( $P < .001$  and  $P < .001$ , respectively).

US alone for detecting central LN metastases.<sup>[15,14]</sup> In the present study, preoperative neck US and neck CT images of PTC patients who underwent total thyroidectomy and central LN dissection were reviewed. Notwithstanding preoperative evaluation results, a considerable number of PTC patients who underwent prophylactic central LN dissection have shown central LN metastases on pathologic reports.<sup>[15,16]</sup> In the present study, 467 (33.2%) patients with clinically node-negative PTC had confirmed pathologic metastases in central LNs, comparable with results of other studies.<sup>[2,17]</sup> Because of the high rate of central LN metastases in clinically node-negative PTC, prophylactic central LN dissection is routinely performed in our institution.

Prophylactic central LN dissection is a main interest in clinically node-negative PTC patients. This dissection could eliminate the source of a recurrence, thereby reducing the need for reoperation. It can benefit decision-making by allowing for the use of accurate nodal information during follow-up. However, prophylactic central LN dissection could increase the possibility of postoperative complications such as hypoparathyroidism and recurrent laryngeal nerve injury. It is considered an overtreatment if pathology has confirmed node-negative PTC with less aggressive tumors. Clinicians need to balance advantages and disadvantages of prophylactic central LN dissection. According to recent guidelines, prophylactic central LN dissection should be considered in patients with clinically central node-negative PTC



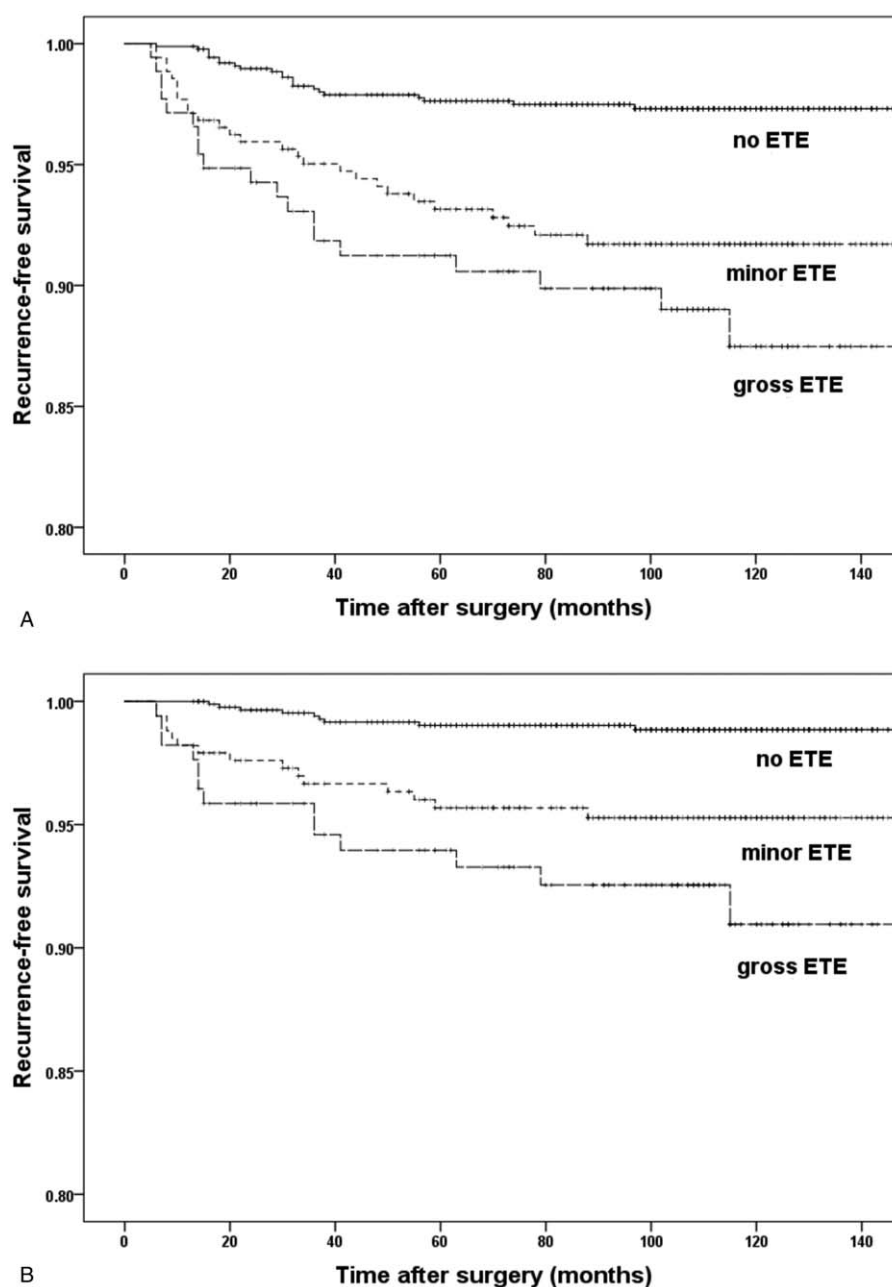
**Figure 2.** Recurrence-free survival curve according to lymph node ratio, (A) all patients, (B) patients with or without recurrence in the lateral neck compartment ( $P < .001$  and  $P < .001$ , respectively).

who have advanced primary tumors (T3 or T4) or cN1b. However, such dissection is not recommended for patients with small (T1 or T2), noninvasive, or clinically node-negative PTC.<sup>[18]</sup>

The number of harvested central LNs is still debatable. Barczynski et al have reported that patients with fewer than 6 central LNs have higher rates of recurrence in the lateral neck compartment than those with 6 or more central LNs in surgical specimens.<sup>[9]</sup> Randolph et al have demonstrated that PTC patients with more than 5 metastatic LNs have markedly greater recurrence risk than those with fewer than 5 metastatic LNs. They suggested that at least 6 LNs should be removed to evaluate the LN status in the central neck compartment.<sup>[19]</sup> Although the

number of harvested LNs was relatively small, the present study showed no correlation between the number of harvested central LNs and recurrence in any lesion or in the lateral neck compartment.

Barczynski et al have found that an LN ratio of more than 0.3 is an independent prognostic factor for lateral neck LN recurrence in PTC patients who have undergone total thyroidectomy and prophylactic central LN dissection.<sup>[9]</sup> Kim et al reported that LN ratio  $> 0.5$  is associated with lateral neck recurrence in PTC patients who underwent total thyroidectomy plus prophylactic or therapeutic central LN dissection without cN1b.<sup>[20]</sup> In another study of 198 PTC patients who underwent total thyroidectomy and neck dissection, patients with LN ratio  $\geq 0.3$  had 3.4 times



**Figure 3.** Recurrence-free survival curve according to extrathyroidal extension, (A) all patients, (B) patients with or without recurrence in the lateral neck compartment ( $P < .001$  and  $P < .001$ , respectively).

higher risk of persistent or recurrent disease than those with ratio of 0.<sup>[21]</sup> However, these studies included different proportions of patients with pathologic N0 and various extents of LN dissection. Therefore, the value of LN ratio depends on the number of patients with pathologic N0. PTC patients with pathologic N1a had clearly worse RFS than those with pathologic N0. In the present study, optimal LN ratio was calculated using a ROC curve among the patients who had confirmed pathologic N1a to decrease heterogeneity. Among these patients, patients with LN ratio of more than 0.55 had worse RFS in the present study. Although LN ratio in PTC is a significant predictor of disease-free survival, multicenter studies are required to set optimal cut-offs and standardize surgical extent.

Although the incidence of PTC is higher in females, 1 study has reported that male PTC patients have worse prognoses than females because of their unhealthy lifestyles and harmful environmental factors such as smoking and drinking.<sup>[22]</sup> Similarly, the present study revealed that male gender could predict recurrence in the lateral neck compartment.

ETE is an important independent prognostic factor for persistent and recurrent thyroid cancer. It was first classified as gross (extension to trachea, larynx, esophagus, recurrent laryngeal nerve, or subcutaneous soft tissue) or minimal (extension to the sternothyroid muscle or perithyroidal soft tissue) based on the 6th AJCC Cancer Staging Manual.<sup>[23]</sup> In the 8th Manual, however, tumor  $>4$ cm in the greatest dimension

**Table 4**  
**Multivariate analyses of patients with or without lateral recurrence according to recurrence.**

	HR	95% CI	P
Sex			
Female	1		
Male	2.217	1.057–4.647	.035
LVI			
No LVI	1		
LVI	2.074	0.625–6.889	.234
Tumor size			
≤ 1cm	1		
>1cm	2.257	1.138–4.476	.020
Pathologic N			
N0	1		
N1a	5.957	2.573–13.789	<.001
ETE			
No ETE	1		
Minor ETE	3.027	1.315–6.966	.009
Gross ETE	4.058	1.685–9.774	.002

CI=confidence interval, ETE=extrathyroidal extension, HR=hazard ratio, LVI=lymphovascular invasion.

limited to the thyroid gland is considered T3a and gross ETE with invasion only to the strap muscles is considered T3b.<sup>[24]</sup> This study showed that patients with gross ETE had high incidence rates of recurrence in any lesion and in the lateral compartment. In recent AJCC recommendations, minor ETE was removed from the definition of T3 disease.<sup>[8]</sup> Interestingly, in the present study, patients with minor ETE had worse RFS than those without ETE.

CLT is an autoimmune thyroid disease characterized by fibrosis, atrophy, and lymphocyte infiltration of thyroid tissue. Several studies have reported that those with CLT have high prevalence of PTC to those without CLT thyroid disease.<sup>[25,26]</sup> Additionally, high TSH levels in patients with thyroid nodules can increase the risk of thyroid malignancy.<sup>[27,28]</sup> However, CLT coexisting with PTC is associated with a lower prevalence of central LN metastasis and a lower risk of recurrence during follow-up.<sup>[29,30]</sup> In the present study, 578 (41.1%) patients had CLT, including 26 patients with recurrence in any lesion (26/68, 38.2%) and 13 patients showing recurrence in the lateral neck compartment (13/37, 35.1%). However, the present study failed to analyze the relationship between CLT and the incidence of PTC because only PTC patients were enrolled. CLT showed no significant difference according to recurrence. We were unable to select the optimal cut-off level of baseline TSH level in ROC curve due to less than 0.5 of area under curve. Further, we found no association between baseline TSH level and recurrence.

**Table 5**  
**Postoperative complications.**

Complication	Number (%)
Hypocalcemia	
Transient	86 (6.1)
Permanent	27 (1.9)
Recurrent laryngeal nerve palsy	
Transient	89 (6.3)
Permanent	8 (0.6)
Bleeding	7 (0.5)

During the follow-up after initial treatment for differentiated thyroid cancer (DTC), TSH suppression therapy may enhance survival outcome of high-risk patients.<sup>[31,32]</sup> According to the 2015 American Thyroid Association (ATA) Management Guidelines, in high-risk DTC patients, the initial TSH level was set at less than 0.1 mU/L.<sup>[18]</sup> For intermediate-risk DTC patients, the initial TSH level was set at 0.1–0.5 mU/L. However, target TSH level in low-risk DTC patients remains controversial. In the current study, we observed 68 patients with recurrent lesion. Among them, 39 (57.4%) patients showed TSH level of less than 0.1 mU/L of at the time of recurrence, even patients with lung metastases had TSH level of 1.6 mU/L. Cancer cells originating in DTC are known to express TSH receptor and TSH can stimulate cancer cell proliferation. However, our study failed to show any relationship between suppressed TSH level and prognosis. Recurrence was defined as a structural disease in this study. Most patients belonged to intermediate- or low-risk group according to ATA guidelines. Further studies are needed to determine the association between suppressed TSH level and prognosis in clearly demarcated PTC patients.

One study of 752 patients with clinically node-negative DTC showed that patients who underwent total thyroidectomy with bilateral routine central LN dissection had higher risk of permanent hypoparathyroidism (3.59% vs 1.03%) and permanent vocal cord palsy (1.65% vs 0.77%) than those who underwent thyroidectomy alone.<sup>[33]</sup> However, there was no significant difference in recurrence during a median follow-up of 9.5 years. Authors of that study suggested that prophylactic central LN dissection should be selectively administered to avoid potential morbidity.<sup>[33]</sup> In contrast, one study reported that permanent nerve injuries occurred in 1/266 (0.4%) while permanent hypoparathyroidism occurred in 4/266 (1.5%) patients.<sup>[34]</sup> Authors of that study supported that bilateral central LN dissection with total thyroidectomy could be safely performed to treat PTC by experienced endocrine surgeons.<sup>[34]</sup> Moo et al reported that there were no significant differences in permanent hypoparathyroidism or recurrent laryngeal nerve injury irrespective of prophylactic central LN dissection.<sup>[35]</sup> However, because of significant differences in recurrence, they advocated routine central LN dissection.<sup>[35]</sup> Our study showed comparable rates (1.9% permanent hypoparathyroidism and 0.6% permanent unilateral recurrent laryngeal nerve injury) with those reported in the above-mentioned study.

Several studies have revealed that extranodal extension (ENE) can increase nodal recurrence and distant metastases.<sup>[36,37]</sup> In addition, Lango et al have reported that ENE can reduce the possibility of complete biochemical response and predict disease progression due to potential tumor persistence.<sup>[38]</sup> Our study had a large number of PTC patients with pathologic N0. Additional studies are needed to evaluate ENE in PTC patients who underwent therapeutic central LN dissection.

This study has several potential limitations. First, the study design was retrospective. In addition, relatively fewer harvested central LNs were used in the present study compared with other studies. We did not consider biochemical incomplete response related to Tg or anti-Tg antibody concentrations during postoperative follow-up. We did not study the influence of postoperative radioactive ablation therapy either. Sufficient clinicopathological data on long-term follow-up results in PTC patients who underwent prophylactic central LN dissection need to be collected for further studies.

In conclusion, prophylactic central LN dissection is a safe procedure for patients with clinically node-negative PTC in the



central compartment. A considerable number of patients who underwent central LN dissection showed confirmed LN metastases on postoperative pathologic reports. Lateral neck LN recurrence in clinically node-negative PTC patients is predicted by male, main tumor size >1 cm, ETE, and nodal factors (pathologic N1a, positive delphian node, and LN ratio). Close monitoring and thorough management are needed for PTC patients with these predictive factors during follow-up.

## Author contributions

**Conceptualization:** Young Jae Ryu and Min Ho Park.

**Data curation:** Young Jae Ryu and Jin Seong Cho.

**Formal analysis:** Jin Seong Cho.

**Investigation:** Young Jae Ryu and Shin Jae Kang.

**Methodology:** Young Jae Ryu.

**Resources:** Young Jae Ryu.

**Software:** Young Jae Ryu and Shin Jae Kang.

**Supervision:** Min Ho Park and Jung Han Yoon.

**Validation:** Jin Seong Cho and Jung Han Yoon.

**Writing – original draft:** Young Jae Ryu.

**Writing – review and editing:** Young Jae Ryu and Min Ho Park.

Young Jae Ryu orcid: 0000-0001-7302-8109.

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