



Number of Metastatic Lymph Nodes and Ratio of Metastatic Lymph Nodes to Total Number of Retrieved Lymph Nodes Are Risk Factors for Recurrence in Patients With Clinically Node Negative Papillary Thyroid Carcinoma

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Objectives. The number of metastatic lymph nodes (LNs) and the ratio between the number of metastatic LNs and the total number of retrieved LNs (the LN ratio [LNR]) have been proposed as risk factors for recurrence of papillary thyroid carcinoma (PTC). However, the significance of the number of LNs and the LNR in patients with clinically node negative PTC has not been clearly determined. The purpose of this study is to evaluate their significance.

Methods. We retrospectively analyzed 382 patients with PTC who had undergone total thyroidectomy with prophylactic central neck dissection (CND) between January 2000 and December 2010. We excluded patients with lobectomy, concurrent lateral compartment neck dissection, a follow-up period less than at least 2 years, number of harvested central LNs less than or equal to one, clinically positive LN, distant metastasis, recurrent cancer or other types of malignancy. The correlations between recurrence and various clinicopathologic characteristics including tumor size, extrathyroidal extension (ETE), stage, number of metastatic central LNs, and the LNR were investigated.

Results. After a mean follow-up period of 82.2 ± 26.4 months, recurrence occurred in 14 patients (3.7%). Tumor size ≥ 20 mm, maximal ETE, presence of central LN metastasis, number of metastatic LNs ≥ 2 , and LNR ≥ 0.31 correlated with recurrence in the univariate analysis. However, tumor size ≥ 20 mm, maximal ETE, number of metastatic LNs ≥ 2 , and LNR ≥ 0.31 were significantly associated with recurrence in the multivariate analysis (hazard ratio=6.61, 7.17, 3.43, and 11.23, respectively).

Conclusion. The LNR and the number of metastatic LNs are independent prognostic risk factors for recurrence in patients with clinically node negative PTC, and these factors can be used to guide postoperative adjuvant therapy and follow-up strategy after prophylactic CND.

Keywords. Lymph Node Metastasis; Papillary Thyroid Cancer; Recurrence; Lymph Node Ratio; Central Neck Dissection

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INTRODUCTION

During the past 20 years, the incidence of thyroid cancer has increased sharply all over the world mainly due to increased detection using ultrasonography [1], and the incidence rate of thyroid cancer in Korea is the highest in the world [2]. The incidence of papillary thyroid carcinoma (PTC) accounts for the majority of this increase [3]. Although patients with PTC have

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excellent prognosis and survival, recurrence occurs in 5%–21% of patients with PTC [4,5]. Recurrence of PTC usually requires a second operation, which carries a higher complication rate, especially if central neck dissection (CND) is necessary. Therefore, the prevention of recurrence is important in the management of PTC to minimize treatment morbidity and improve both quality of life and survival rate.

Tumor size, extrathyroidal extension (ETE), age, lymph node (LN) metastasis, tumor multiplicity, extranodal spread, and male sex are all associated with increased risk of recurrence of PTC [6-8]. LN metastasis occurs in 20%–90% of patients with PTC [9-11], and is associated with increased recurrence and decreased survival in patients with PTC [12,13]. Recently, the number of metastatic LNs and the ratio of metastatic LNs to the total number of retrieved LNs (the LN ratio [LNR]) have been suggested as prognostic risk factors for recurrence in patients with PTC [14-21]. However, the clinical significance of these measures in patients with clinically node negative (cN0) PTC has not yet been established clearly. The aim of this study is to evaluate the prognostic significance of the number of metastatic LNs and the LNR of central compartment LNs in patients with cN0 PTC.

MATERIALS AND METHODS

Patients

We reviewed retrospectively the data from 382 patients with PTC who underwent total thyroidectomy with prophylactic CND between January 2000 and December 2010. Bilateral CND was performed in 258 patients (67.5%) and unilateral CND in 124 patients (32.5%). We excluded patients who had clinically positive LN metastasis in preoperative work-up, who underwent lobectomy or concurrent lateral compartment neck dissection, or patients with a follow-up period of less than at least 2 years, the number of harvested LNs less than or equal to one, recurrent tumor, distant metastasis, other types of malignancy or history of thyroid surgery or irradiation. This study was approved by the Institutional Review Board of Hanyang University Hospital (IRB No. 2017-09-028) and the informed consent was waived. We conducted this study in compliance with the

HIGHLIGHTS

- This retrospective study examined the risk factors of recurrence after total thyroidectomy in 382 clinically node negative papillary thyroid carcinoma patients.
- Tumor size, extrathyroidal extension, number of metastatic lymph node (LN), and LN ratio (LNR) were the independent factors for recurrence.
- LNR ≥ 0.31 was associated with an 11.2-fold increased risk of post-thyroidectomy recurrence.

principles of the Declaration of Helsinki.

Radioactive iodine (RAI) ablation at a dose of 30 to 150 mCi was performed 2 to 4 months postoperatively. RAI ablation was performed in all patients with gross ETE, or a tumor size larger than 4 cm, or distant metastases. RAI ablation was also recommended for selected patients with minimal ETE or cervical LN metastasis and tumor size 1 to 4 cm and/or higher risk histologic features similar to American Thyroid Association guidelines [22].

Physical examination, neck ultrasonography, serum thyroid-stimulating hormone-stimulated or thyroid-stimulating hormone-suppressed thyroglobulin (Tg) measurements, and anti-Tg antibody measurements were used to detect recurrence of PTC after surgery at 6 to 12-month intervals. Computed tomography, whole-body iodine scan, or fluorodeoxyglucose-positron emission tomography-computed tomography were also used to detect recurrence if necessary. Recurrence was defined as the development of new abnormal structural lesions identified by one of the imaging methods mentioned previously, and was confirmed pathologically using fine needle aspiration cytology.

Number of LN metastases and the LNR

The whole thyroid gland and the central LNs removed were analyzed histopathologically to evaluate tumor characteristics, including tumor size, multiplicity, bilaterality, lymphatic or vascular invasion, ETE, the total number of LNs, and the number of metastatic LNs. The LNR was defined as the total number of metastatic LNs divided by the total number of LNs retrieved from the central compartment.

Statistical analyses

The cutoff values for the number of metastatic LNs and the LNR were determined when sensitivity and specificity were optimized using receiver operating characteristic curve analysis.

The correlation of recurrence of PTC with various clinicopathologic factors, including age, sex, tumor size, ETE, multiplicity, bilaterality, TNM (tumor, node, and metastasis) classification stage, number of metastatic LNs and the LNR was analyzed using Pearson's chi-square test and Fisher exact test. Factors that were statistically significant in the univariate analysis were further analyzed by multiple logistic regression.

Recurrence-free survival (RFS) curves were calculated using the Kaplan-Meier method and compared using the log-rank test. A *P*-value less than 0.05 was considered to be statistically significant. All statistical analyses were performed using IBM SPSS ver. 21.0 (IBM Corp., Armonk, NY, USA).

RESULTS

Patients and tumor characteristics

The clinicopathologic characteristics are summarized in Table 1. The study included 55 men and 327 women, and the mean age

was 47.8 ± 12.5 years. The mean tumor size was 12.0 ± 8.1 mm. Minimal ETE (e.g., tumor extension to the sternothyroid muscle or perithyroidal soft tissues) was found in 174 patients (45.5%), and maximal ETE (e.g., tumor extension to the trachea, esophagus, recurrent laryngeal nerve, larynx, pharynx, subcutaneous soft tissue, or skin) was found in 15 patients (3.9%).

Central LN metastasis was confirmed in 144 patients (37.7%) in the final pathologic report. The mean number of harvested and metastatic central LNs was 7.14 ± 6.23 (range, 2 to 40) and 1.13 ± 2.35 (range, 1 to 21), respectively, and the mean LNR

Table 1. Clinicopathologic characteristics and surgical outcome of the papillary thyroid carcinoma patients who underwent total thyroidectomy with prophylactic central neck dissection

Characteristic	Value (n=382)
Sex (female:male)	327:55
Age (yr)	47.8 ± 12.5
Tumor size (mm)	12.0 ± 8.1
Minimal ETE	174 (45.5)
Maximal ETE	15 (3.9)
Lymphovascular invasion	50 (13.1)
Multiplicity	92 (24.1)
Bilaterality	71 (18.6)
Stage (I:II:III:IV)	232:0:139:11
T classification (T1:T2:T3:T4)	194:0:173:15
N classification (N0:N1a)	238 (62.3):144 (37.7)
No. of harvested LNs	7.14 ± 6.23
No. of metastatic LNs	1.13 ± 2.35
LNR	0.18 ± 0.30
Radioactive iodine	289 (75.7)
Follow-up period (mo)	82.2 ± 26.4
Recurrence	14 (3.7)

Values are presented as mean \pm standard deviation or number (%). ETE, extrathyroidal extension; LN, lymph node; LNR, LN ratio.

was 0.18 ± 0.30 . Postoperative RAI ablation was performed in 289 patients (75.7%).

Of the 382 patients, 14 (3.7%) suffered recurrence during the mean follow-up period of 82.2 ± 26.4 months. Seven patients had recurrence in the lateral compartment LN, six patients in the central neck, and one in a distant site (the lung). The patient with metastasis in the lung died from the disease.

Cutoff values for number of metastatic LNs and the LNR

The cutoff value for the number of metastatic LNs was two, with a sensitivity of 42.9% and a specificity of 79.3% (area under curve, 0.728; standard error, 0.069). The cutoff value for the LNR was 0.31, with a sensitivity of 71.4% and a specificity of 77.4% (area under curve, 0.776; standard error, 0.072) (Fig. 1).

Factors associated with recurrence

The univariate and multivariate correlations between clinicopathologic characteristics and recurrence is presented in Tables 2 and 3, respectively. In the univariate analysis, tumor size ≥ 20 mm, maximal ETE, the presence of central LN metastasis, the numbers of metastatic central LNs ≥ 2 , and a central LNR ≥ 0.31 were associated statistically with recurrence (Table 2).

In the multivariate analysis, tumor size ≥ 20 mm, maximal ETE, the number of metastatic LNs ≥ 2 , and a central LNR ≥ 0.31 were associated statistically with recurrence, whereas the presence of central LN metastases showed no statistical significance (Table 3). The hazard ratios for the number of metastatic LNs ≥ 2 and central LNR ≥ 0.31 were 3.43 (95% confidence interval [CI], 1.04 to 11.26) and 11.23 (95% CI, 2.81 to 44.82), respectively.

Recurrence-free survival

The 10-year RFS rate was 96.0%. The RFS rate was significantly decreased in patients with tumor size ≥ 20 mm (97.8% vs.

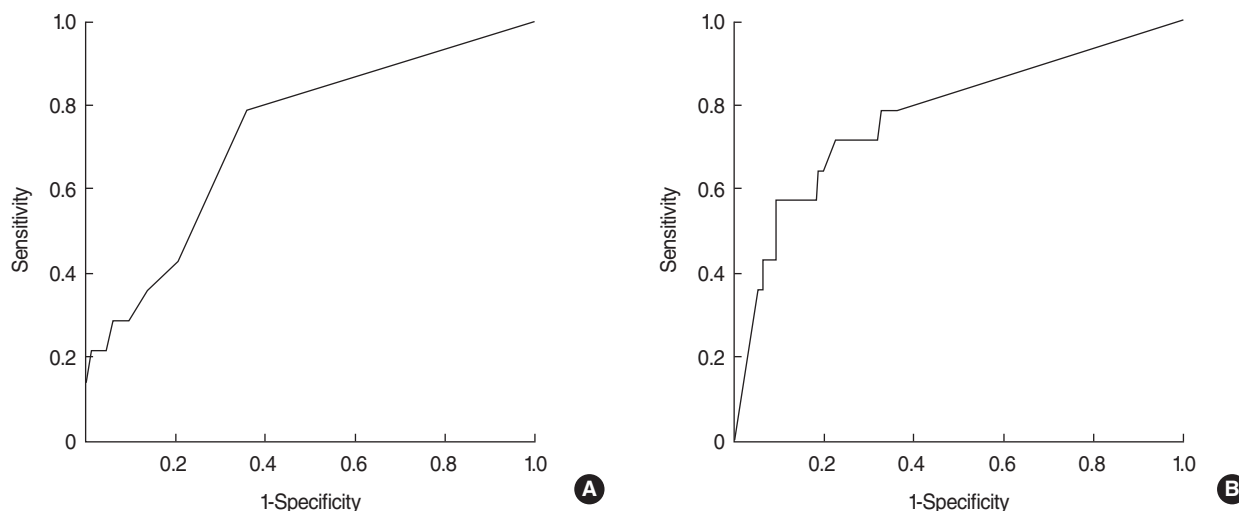


Fig. 1. Receiver operating characteristic curve for recurrence of papillary thyroid cancer. (A) Number of metastatic lymph nodes (LNs), (B) LN ratio of metastatic LNs to the total number of recovered LNs in the central compartment.

Table 2. Univariate analysis for factors related to recurrence in patients with clinically node negative papillary thyroid carcinoma (n=382)

Variable	Recurrence (-) (n=368)	Recurrence (+) (n=14)	P-value
Tumor size ≥ 20 mm			<0.001
Yes	59	9	
No	309	5	
Sex			0.236
Female	313	14	
Male	55	0	
Age ≥ 45 yr			0.576
Yes	239	8	
No	129	6	
Minimal ETE			0.288
Yes	180	9	
No	188	5	
Maximal ETE			0.001
Yes	11	4	
No	357	10	
Lymphovascular invasion			0.231
Yes	50	0	
No	318	14	
Multiplicity			1.0
Yes	89	3	
No	279	11	
Bilaterality			0.730
Yes	68	3	
No	300	11	
Stage			0.402
1/2	225	7	
3/4	143	7	
T classification			0.286
1/2	189	5	
3/4	179	9	
Central LNM			0.039
Yes	136	9	
No	232	5	
No. of central LNM ≥ 2			0.047
Yes	76	6	
No	292	8	
Central LNR ≥ 0.31			<0.001
Yes	83	10	
No	285	4	

ETE, extrathyroidal extension; LNM, lymph node metastasis; LNR, lymph node ratio.

87.8%, $P < 0.001$), maximal ETE (96.9% vs. 75.0%, $P < 0.001$), number of metastatic LNs ≥ 2 (97.1% vs. 93.7%, $P = 0.025$) and central LNR ≥ 0.31 (98.5% vs. 88.6%, $P < 0.001$) (Fig. 2).

DISCUSSION

Prophylactic CND remains still controversial in patients with cN0 PTC. Arguments against prophylactic CND include a lack of

Table 3. Multivariate analysis for factors related to recurrence in patients with clinically node negative papillary thyroid carcinoma

Variable	P-value	Hazard ratio	95% CI
Tumor size ≥ 20 mm	0.004	6.61	1.82–23.98
Maximal ETE	0.010	7.17	1.61–31.87
Central LNM	0.104	2.14	0.62–64.85
Central LNM ≥ 2	0.042	3.43	1.04–11.26
LNR ≥ 0.31	0.001	11.23	2.81–44.82

CI, confidence interval; ETE, extrathyroidal extension; LNM, lymph node metastasis; LNR, lymph node ratio.

substantial evidence of the benefit and the potential morbidity of the procedure [11,23]. However, prophylactic CND may LN recurrence, and it provides more accurate staging for decisions regarding adjuvant RAI ablation [24,25]. The aim of this study was to evaluate the clinical significance of the number of metastatic central LNs and the LNR of metastatic LNs to the total number of retrieved LNs in patients with PTC who underwent total thyroidectomy and prophylactic CND. Prophylactic CND would be very useful to decide postoperative strategies if the information obtained after prophylactic CND such as the presence of LN metastasis, the number of positive LN, and LNR can be prognostic factors related to the recurrence.

In the current study, we found that a central LNR of 0.31, two or more metastatic central LNs, tumor size ≥ 20 mm and maximal ETE were independent risk factors for recurrence, whereas the presence of metastatic central LNs was not related to recurrence in multivariate analysis. The hazard ratio of LNR ≥ 0.31 was 11.23 (95% CI, 2.81 to 44.82), and it is higher than central LN metastasis ≥ 2 , tumor size ≥ 20 mm, and maximal ETE (hazard ratio=3.43, 6.61, and 7.17, respectively). The LNR seems to be a promising prognostic factor for recurrence in patients with cN0 PTC.

The clinical significance of the number of metastatic LNs for patients with PTC remains unclear, especially in cN0 PTC. Some investigators suggested that the number of metastatic LNs is a significant predictive factor for disease recurrence [14,15]. Sugitani et al. [14] demonstrated that the risk of recurrence was significantly higher in PTC patients with five or more metastatic LNs (19%) than in those with fewer than five metastatic LNs (8%). Park et al. [15] also reported that the number of metastatic central compartment LNs (>3 metastatic LNs) in PTC was a significant predictor for recurrence conferring a hazard ratio of 1.36 (95% CI, 1.103 to 1.680). In the current study, two or more metastatic central LNs were an independent risk factor for recurrence in cN0 PTC by multivariate analysis. However, some authors have reported that the number of metastatic LNs was not associated with recurrence [21,26]. Wang et al. [26] reported that higher T stage, increased number of metastatic LNs, increased LN diameter, and presence of extranodal spread were related to recurrence in differentiated thyroid carcinoma in univariate analysis. However, in multivariate analysis, extranodal

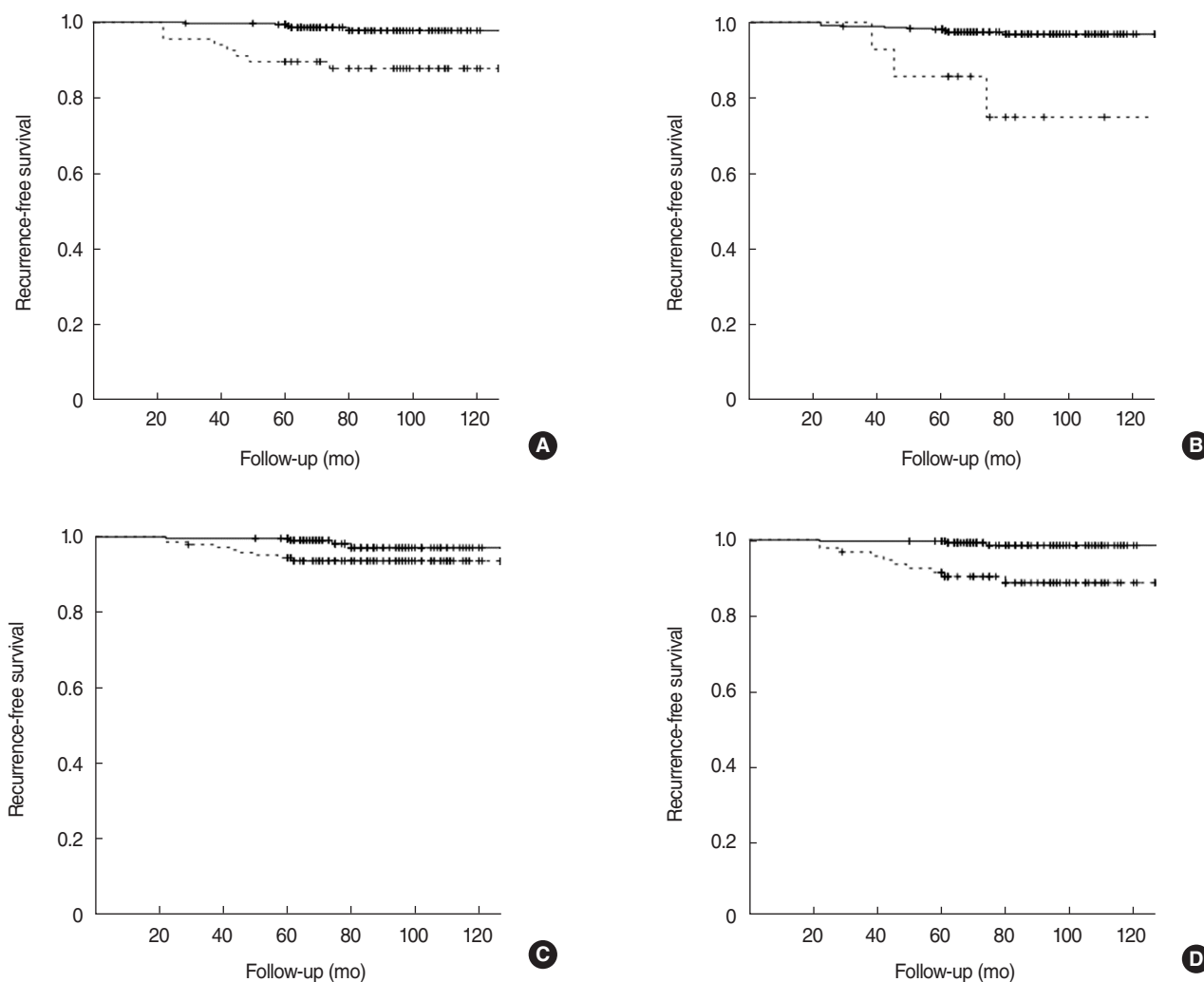


Fig. 2. Kaplan-Meier plot showing recurrence-free survival by (A) tumor size ≥ 20 mm, (B) maximal extrathyroidal extension, (C) number of metastatic lymph nodes ≥ 2 , and (D) central lymph node ratio ≥ 0.31 .

spread was the only statistically significant factor, and the number of metastatic LNs was not associated with recurrence [26]. Ryu et al. [21] also demonstrated by multivariate analysis that the number of metastatic LNs was not an independent risk factor for recurrence in pathologic N1a PTC. Further studies might be necessary to clarify the impact of number of LN metastases on the risk of recurrence in PTC considering all previous studies.

The LNR is likely to be an important prognostic factor for risk of recurrence in the previous studies. Several authors have assessed the relationship between the LNR and recurrence in patients with PTC, and reported that LNR was an important risk factor for recurrence although, in fact, the cutoff values for the LNR range from 0.26 to 0.86 in different studies [16-21,27-30]. Vas Nunes et al. [16] reported that PTC patients with an LNR of 0.30 or higher had a 3.4 times higher risk of persistent or recurrent disease compared with patients with an LNR of 0.00. In other study, LNR ≥ 0.86 in the central compartment had signifi-

cantly worse disease-free survival rates than patients with ratios below these threshold values [17]. Jeon et al. [18] reported that LNR (higher than 0.4) and size of metastatic nodes were significant prognostic factors in pathological N1a PTC. Yip et al. [19] also demonstrated that the LNR independently predicted PTC recurrence. Schneider et al. [20] found that a LNR ≥ 0.42 is the best cutoff value to divide those with LN metastasis based on disease-specific survival in the study of 10,995 PTC patients utilizing the surveillance, epidemiology, and end results (SEER) database. Choi et al. [27] reported that the LNR of 0.44 is a predictive factor for the loco-regional recurrence in patients with papillary thyroid microcarcinoma. Lee et al. [28] analyzed both central and lateral compartment LNRs: it reported that cutoff values of 0.4 and 0.5 for central LNR and total LNR, respectively, were significant risk factors for recurrence of PTC. However, Beal et al. [29] analyzed 9,926 patients with differentiated thyroid carcinoma in the SEER database, and showed that the LNR

was not associated with overall survival in the pathologic N1 patients.

There are few reports that evaluated the significance of LNR in prophylactic CND for PTC. Ryu et al. [21] demonstrated that an LNR >0.65 in the central compartment was the only independent factor for recurrence in pathologic N1a PTC after prophylactic CND. Lee et al. [30] also showed that an LNR ≥ 0.26 was an independent predictor of regional LN metastasis recurrence in patients with PTC who underwent total thyroidectomy and bilateral prophylactic CND. In the current study, an LNR of ≥ 0.31 was an independent predictor of recurrence in patients with cN0 PTC who underwent total thyroidectomy and prophylactic CND.

The differences of the LNR and the number of metastatic LNs between previous studies might be related to difference in study cohorts, cutoff values for metastatic LNs and LNR, LN yields, accuracy of pathologic examination, and follow-up period. Some studies analyzed only patients with central compartment LN metastasis, whereas other workers included patients with both central and lateral LN metastasis, which might be related to more advanced disease and worse prognosis. We excluded patients who underwent concurrent lateral compartment LN dissection and included only the homogenous prophylactic CND group. The total LN yield via CND might be influenced by the extent of LN dissection and accuracy of pathologic examination. Therefore, high and low yields of LNs might be defined differently in different studies, although the LNRs might be similar. In the current study, we performed compartment-oriented CND routinely, including pretracheal, paratracheal and prelaryngeal LN groups in most patients. The mean number of harvested LNs was 7.14 ± 6.23 , which we consider to be adequate, indicating that CND was carried out correctly. We also included only those patients from whom at least two central LNs were harvested. To minimize bias and differences between studies, standardized cutoff values for the LNR and number of metastatic LNs are needed. In addition, the follow-up period differed between the studies. In some studies, the follow-up period was in the region of 5 years; however, a long-term follow-up of more than 10–20 years is necessary for accurate evaluation of recurrence and survival in patients with PTC.

There are some limitations to the current study. It is a retrospective study performed in a single center and might be influenced by a selection bias. The diverse LN yield (range, 2 to 40) during CND might also cause bias in the results, although we routinely performed compartment-oriented CND. The relatively short follow-up period is also another drawback. The mean follow-up period was 82.2 ± 26.4 months, which might not be long enough to determine all recurrences, although most recurrences occurred within 5–10 years. A further prospective cohort study including larger numbers of homogenous patients with long-term follow up is necessary to overcome the limitations of this study.

In conclusion, tumor size ≥ 20 mm, maximal ETE, two or

more metastatic central LNs, and an LNR ≥ 0.31 are independent predictors for recurrence in patients with cN0 PTC. A LNR ≥ 0.31 and number of metastatic LNs greater than or equal to two might be used as prognostic indicators after prophylactic CND to guide postoperative adjuvant therapy and follow-up strategy.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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