



Right posterior paratracheal lymph nodes metastasis is one of the predictive factors in right-sided papillary thyroid carcinoma

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ABSTRACT

Background: Lymph nodes in the right paratracheal region are separated as anterior and posterior on the basis with right recurrent laryngeal nerve. Dissection of the right posterior paratracheal lymph nodes is sometimes overlooked during a central neck dissection. Therefore, this study was designed to assess the clinicopathologic risk factors and prognostic implication for recurrence related to the presence of right posterior paratracheal lymph nodes metastasis in patient with right-sided papillary thyroid carcinoma. **Methods:** Records from 763 patients with papillary thyroid carcinoma who underwent total thyroidectomy with central neck dissection, including the right posterior paratracheal lymph nodes, between January 2007 and March 2015 were reviewed retrospectively.

Results: Among 763 patients (120 men and 643 women; mean age 49.04 years) with right-sided papillary thyroid carcinoma, 127 exhibited right posterior paratracheal lymph nodes metastases. In multivariate analysis, central-compartment lymph nodes metastases (odds ratio 5.203; 95% confidence interval, 2.864–9.453) and lateral cervical lymph nodes metastases (odds ratio 3.668; 95% confidence interval, 2.375–5.667) were independently correlated with right posterior paratracheal lymph nodes metastases. Twenty-three patients (3.0%) showed loco-regional recurrence. The loco-regional recurrence rate was greater in the groups for males ($P = .012$), larger tumor size (>10 mm; $P = .044$), extrathyroidal extension ($P = .002$), and right posterior paratracheal lymph nodes metastasis ($P < .001$).

Conclusion: Right posterior paratracheal lymph nodes metastases are predictive factors of loco-regional recurrence, and these lymph nodes should be removed completely during a right central neck dissection in patients with right-sided papillary thyroid carcinoma with central or lateral cervical lymph node metastasis.

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Introduction

Papillary thyroid carcinoma (PTC) is the most common thyroid cancer, accounting for $>90\%$ of all thyroid cancer. Generally, PTC has a good prognosis with 10-year survival rates of $\geq 90\%$.¹ Cervical lymph node (LN) metastases are quite common in PTC.² Although controversy remains regarding the clinical importance of LN metastasis, cervical LN metastases are known to be one of the important predictive factors for loco-regional metastases.^{3,4}

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The right recurrent laryngeal nerve travels through the fibrofatty tissue of the right paratracheal LNs, a different course from the left recurrent laryngeal nerve. There are some lymph nodes between the right recurrent laryngeal nerve and the esophagus or prevertebral fascia, which are called as right (upper) paraesophageal lymph nodes.^{1,2,5} Agrawal et al⁶ recently classified lymph nodes in the right paratracheal region as anterior and posterior components on the basis of right RLN. The posterior component of right paratracheal lymph nodes and the right upper para-esophageal lymph nodes are the same region (Fig 1).

Some studies have showed that the posterior component of right paratracheal lymph nodes should ideally be removed and that is of specially concern because it is a common and unfavorable place for disease recurrence.^{7–9} Dissection of the right posterior

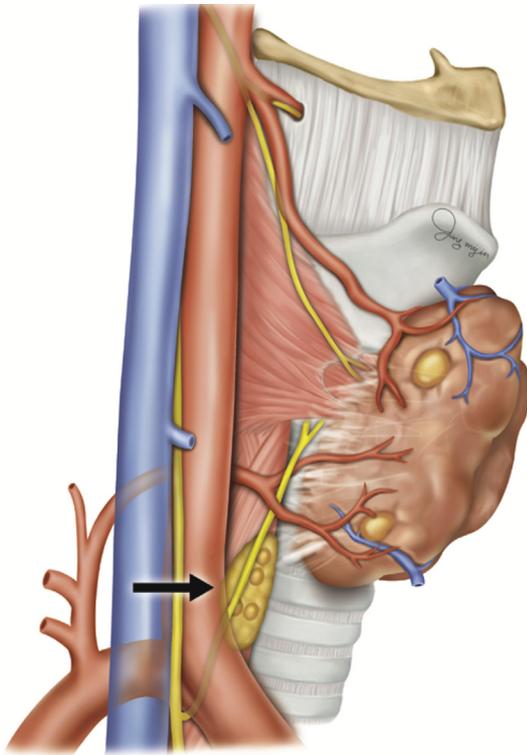


Fig 1. Schematic diagram indicating the location of the posterior paratracheal lymph nodes (black arrow). The right recurrent laryngeal nerve travels through the fibrofatty tissue of the right paratracheal lymph nodes, a different course from the left recurrent laryngeal nerve. There are some lymph nodes between the right recurrent laryngeal nerve and the esophagus or prevertebral fascia.

paratracheal lymph nodes, however, is sometimes overlooked during a right central neck dissection (CND) because of the possibility of injury to the recurrent laryngeal nerve or bleeding owing to traction and elevation during the removal of these LNs.^{1–6} Although there are some studies about the incidence and risk factors of right posterior paratracheal LNs metastasis (right upper para-esophageal LNs metastasis), there is no study exploring the prognostic importance of nodal metastases in these nodes.^{1,2,5} To clarify the clinical importance of why the right posterior paratracheal LNs should be included in the routine CND, the present study was designed to assess the clinic-pathologic risk factors and prognostic implication for recurrence related to the right posterior paratracheal LNs metastasis in patients with right-sided PTC.

Methods

Patients

We reviewed retrospectively the medical records of 763 patients (643 women and 120 men; mean age, 49.1 years; age range: 13–86 years) who underwent total thyroidectomy with prophylactic CND for PTC with or without lateral neck lymph node dissection, including the right posterior paratracheal LNs at the Department of Otorhinolaryngology-Head and Neck Surgery, Pusan National University Hospital, Pusan, Korea, from January 2007 to March 2015. All primary tumors were located in the right thyroid gland. We performed a total of 4,893 thyroid operations during this time, and the number of patients who received total thyroidectomy with right posterior paratracheal LN dissection was 1,138. Among these 1,138 patients, 763 patients had right-dominant thyroid cancer.

This review analysis was conducted under the approved guidelines of our institutional review board. Procedures for follicular, medullary, and anaplastic thyroid carcinoma were excluded from this analysis. All tumors were confirmed to be primary PTC by postoperative biopsy in accord with intraoperative frozen section biopsy. In cases of multifocal tumors, the tumor with the largest size was chosen as the primary tumor. Preoperative assessment for cervical LN metastasis included high-resolution ultrasonography, fine-needle aspiration cytology, and computerized tomography. Ultrasonography performed by surgeon before the operation evaluated the primary tumor and the cervical status of lymph nodes. One hundred forty-seven patients required lateral or modified radical neck dissection.

Operative technique

All patients underwent total thyroidectomy with routine CND. The dissection was performed according to a technique similar to that described by Grodski et al.⁷ Our technique for CND is as follows: the recurrent laryngeal nerve is usually identified distally near the lower border of the cricothyroid muscle. After the thyroid is removed, the nerve is dissected retrograde to the point where it courses under the clavicles, the innominate artery, or the right carotid artery. The fibrofatty tissues are dissected off the nerve and usually reflected medially and then dissected off the trachea. If possible, the specimen is removed en bloc; additional nodal contents that are deep to the right recurrent laryngeal nerve may be removed separately. If preoperative assessments (ultrasonography, fine-needle aspiration cytology, and computed tomography) were suspicious for cervical LN metastasis, a lateral or modified radical neck dissection is performed. Attention is given in particular to identification of the parathyroid glands, and auto-transplantation of the parathyroid glands is performed only in cases in which their vascularity is compromised.

Lymph node compartments

The CLNs were divided into 3 nodal sites: left paratracheal LNs, right anterior paratracheal LNs, and right posterior paratracheal LNs. The LNs were classified by the operating surgeon. A site was considered positive when one or more nodes in the particular site were reported to contain a tumor.

Statistical analysis

Statistical analysis was performed using SPSS, version 19.0 (SPSS Inc., Chicago, IL). Student's *t* test, Pearson χ^2 test, and Fisher exact test were used to assess the relation between right posterior paratracheal LN metastasis and the following potential risk predictors: sex, age, tumor size, pathologic extra thyroidal extension (ETE), multifocality, T stage, and the number of central and lateral cervical LN metastases. Multivariate analysis was performed using logistic regression analysis. Recurrence survival rates were evaluated using Kaplan-Meier analysis, including the log-rank test, and recurrence time periods were calculated in months from the date of thyroidectomy to the date of any recurrence or last follow-up.

Results

Clinicopathologic characteristics

A total of 763 patients were included in this study (120 men and 643 women; mean age 49.0 years). The clinic-pathologic characteristics of the patients are shown in Table 1. The mean tumor size was 10.4 ± 7.6 mm. Multifocal lesions were identified in

Table I
Clinico-pathologic characteristics of patients who underwent total thyroidectomy with routine central neck dissection

Characteristics	No. of patients (%)
Sex	
Male	120 (15.7)
Female	643 (84.3)
Age, mean	49.1 (± 12.5)
<45	263 (34.5)
≥ 45	500 (65.5)
Tumor size, mean	10.4 (± 7.6)
≤ 10 mm	479 (62.8)
>10 mm	283 (37.1)
Multifocal lesion	
(-)	616 (80.7)
(+)	147 (19.3)
Extrathyroid extension	
Negative	352 (46.1)
Positive	411 (53.9)
T stage	
T1a	251 (32.9)
T1b	59 (7.7)
T2	14 (1.8)
T3	428 (56.1)
T4	11 (1.4)
N stage	
0	266 (34.9)
1a	346 (45.3)
1b	151 (19.8)
No. of removed right posterior paratracheal LN	
-2	401 (52.6)
3-4	218 (28.5)
≥ 5	144 (18.9)
No. of positive right posterior paratracheal LN	
1	88 (11.5)
2	26 (3.4)
≥ 3	13 (1.7)

19.3% (147 of 763) of patients, and ETE was observed in 53.9% (411 of 763). Positive lateral cervical LN metastasis occurred in 19.8% (151 of 763). Assessment of the primary tumor stage showed a T1a lesion in 252 cases (32.9%), a T1b lesion in 59 cases (7.7%), a T2 lesion in 14 cases (1.8%), a T3 lesion in 428 cases (56.1%), and a T4 lesion in 11 cases. The mean number of removed right posterior paratracheal LNs was 3 ± 2 . Among the 763 patients who underwent CND, 127 (16.6%) patients were positive for right posterior paratracheal LN metastasis (Table I). All right posterior paratracheal LNs metastases were unidentified as pathologic microscopic metastases before operation. In our study, the TNM classification was based on seventh edition of the American Committee on Cancer staging system.

Postoperatively, unilateral vocal cord paralysis occurred in 10 patients (1.3%). All patients with postoperative vocal fold paralysis had disease that had invaded the RLN. There was no postoperative vocal fold paralysis associated with the dissection of the right posterior paratracheal LNs. Five patients showed functional recovery of vocal cord movement, but the other 5 patients had no return of RLN function to normal during follow-up.

Risk factors for right posterior paratracheal lymph node metastasis

Univariate analysis of the clinic-pathologic factors associated with right posterior paratracheal LN metastasis was conducted for 763 patients (127 patients with right posterior paratracheal LN metastasis and 636 patients without posterior paratracheal LN metastasis; Table II). Right posterior paratracheal LN metastasis

Table II
Univariate analysis of the clinico-pathologic factors associated with right posterior paratracheal lymph nodes metastasis

		Status of right posterior paratracheal lymph node		P value
		Metastasis (-) n = 636	Metastasis (+) n = 127	
Sex				
	Male	86	34 (28.3%)	.001
	Female	550	93 (14.5%)	
Age				
	<45	212	51 (19.4%)	.140
	≥ 45	424	76 (15.2%)	
Multifocal lesion				
	(-)	509	107 (17.4%)	.271
	(+)	127	20 (13.6%)	
T stage				
	T1a	227	24 (9.6%)	.006
	T1b	46	13 (22%)	
	T2	10	4 (28.6%)	
	T3	344	84 (19.6%)	
	T4	9	2 (18.2%)	
Tumor size (mean mm)		9.7 ± 7.1	13.8 ± 9.01	
	≤ 10 mm	424	55 (11.5%)	.001
	>10 mm	211	72 (25.4%)	
Extrathyroidal extension				
	Negative	307	45 (12.8%)	.008
	Positive	329	82 (20.0%)	
Central LN metastasis				
	Negative	310	14 (4.3%)	.001
	Positive	326	113 (25.7%)	
Lateral LN metastasis				
	Negative	541	71 (11.6%)	.001
	Positive	95	56 (37.1%)	

was associated with sex, tumor size (>10 mm), ETE, T stage, and central and lateral cervical LN metastasis ($P < .05$ each). Age and multifocal lesions did not show any associations. Patients with large tumor size (>10 mm) were more likely to have a metastatic lesion in this area ($P < .001$). The prevalence of right posterior paratracheal LN metastasis in patients with large tumor size (>10 mm) was 25.4%. The rate of right posterior paratracheal LN metastasis was greater in patients with ETE. In multivariate analysis, male sex and right anterior paratracheal LN and lateral cervical LN metastasis were statistically significant independent predictors of right posterior paratracheal LN metastasis (Table III).

Correlation between lateral neck lymph node metastasis and right posterior paratracheal LN metastasis

We divided our 763 patients into 3 groups: group A ($n = 310$), with both negative metastasis to right anterior paratracheal LNs and right posterior paratracheal LNs; group B ($n = 326$), with positive metastasis to right anterior paratracheal LNs only with negative right posterior paratracheal LNs metastasis; and group C ($n = 127$), with positive metastasis to right posterior paratracheal LNs, with positive or negative metastasis to right anterior paratracheal LNs. LLN metastasis was identified in 147 patients, with rates of 7.1% (22 of 310) in group A, 22.4% (73 of 326) in group B, and 44.1% (56 of 127) in groups C (Table IV). Comparison of group A with B or group A with C revealed differences in the rates of LLN metastasis in each group, with odds ratios of 3.777 (95% confidence interval [CI], 2.278–6.263) and 10.325 (95% CI, 5.913–18.028; $P < .001$, respectively; Table V). In addition, the rate of LLN metastasis increased according to the number of right posterior paratracheal LNs metastasis (Fig 2).

Table III

Multivariate of logistic regression analysis for risk factors of right posterior paratracheal lymph nodes metastasis

Variable	P value	Odds ratio (95% CI)
Sex	.002	0.468 (0.289–0.758)
Age	.521	0.873 (0.575–1.323)
Size (>10 mm)	.060	1.505 (0.982–2.304)
Multifocality	.241	0.721 (0.417–1.247)
Extrathyroidal extension	.287	1.871 (0.590–5.934)
Central cervical LN metastasis	<.001	5.203 (2.864–9.453)
Lateral cervical LN metastasis	<.001	3.668 (2.375–5.667)

Correlation between loco-regional recurrence rate and right posterior paratracheal LNs metastasis

To date, 23 patients (3%) have shown loco-regional recurrence. Most recurrent tumors were found by ultrasonography. The median follow-up period was 49.2 months (8.3–116.7), and the median time to recurrence was 26.0 months (8.3–91.4). Fifteen of 23 patients experienced a recurrence in the lateral neck compartment, 5 of 23 patients experienced a recurrence in the central compartment, and 3 patients experienced recurrence in both regions. Ten of 15 patients with only lateral neck recurrence underwent lateral cervical neck dissection at the initial operation. Eighteen patients underwent subsequent revision CND or lateral neck lymph node dissection. Three patients have been under continuous observation without operative intervention because they refused such intervention. One patient experienced distant metastasis in the lung during the follow-up period, and one patient died of anaplastic change recurrence.

Kaplan-Meier curves showed recurrence-free survival rates according to groups based on various patient characteristics, such as age, sex, tumor size, ETE, lateral LN metastasis, and right anterior paratracheal LN metastasis and posterior paratracheal LN metastasis (Fig 3). The loco-regional recurrence rate was significantly greater in the groups with male sex ($P = .012$), larger tumor size (>10 mm; $P = .044$), ETE ($P = .002$), and right posterior paratracheal LN metastasis ($P < .001$).

Discussion

Although there has been much debate about the relationship between CLN metastasis and the clinical impact on survival in patients with PTC, some data have suggested that prophylactic CND during the initial operation may decrease the recurrence of PTC and likely improves disease-specific survival.^{1,10} Because the CLNs are generally the first and most commonly involved nodes with metastasis, there may be a risk of recurrence in these LNs.¹¹ For this reason, there have been many studies on prophylactic CLN

Table IV

Rate of lateral neck LN metastasis related with each group

Variable	Lateral neck LN metastasis
Group A	7.1% (22/310)
Group B	22.4% (73/326)
Group C	44.1% (56/127)

Group A, both negative right anterior and posterior paratracheal LNs metastasis. Group B positive (+) right anterior paratracheal LNs metastasis with negative (-) right posterior paratracheal LNs metastasis. Group C Positive (+) right posterior paratracheal LNs metastasis with positive or negative right anterior paratracheal LNs metastasis.

Table V

Correlation between central lymph node metastasis and lateral neck lymph node metastasis

	B	SE	Wald	P value	Exp (B)	CI (95%)	
						Lower	Upper
Group A			67.586	<.001			
Group B	1.329	.258	26.528	<.001	3.777	2.278	6.263
Group C	2.335	.284	67.397	<.001	10.325	5.913	18.028
Constant	-2.572	.221	135.197	<.001	0.076		

Group A right anterior and posterior paratracheal LNs metastasis (-). Group B right anterior paratracheal LNs metastasis (+) with right posterior paratracheal LNs metastasis (-). Group C right posterior paratracheal LNs metastasis (+) with or without right anterior paratracheal LNs metastasis.

dissection, but there have been few studies regarding right posterior paratracheal LNs.

Right posterior paratracheal LNs lie posterior to the right recurrent laryngeal nerve. Although several studies have recommended that right posterior paratracheal LNs should be removed during a routine CND, the dissection of right posterior paratracheal LNs is sometimes overlooked because of the operative risk and lack of evidence regarding clinical importance. There have been some studies examining the dissection of right posterior paratracheal LNs and the incidence and predictive factors of metastasis to these LNs.^{1–4,6} The rate of right posterior paratracheal LN metastasis in patients with PTC ranged from 5.8% to 26.7% in previous studies.^{1–4,6} In the present study, the incidence of right posterior paratracheal LN metastasis was 16.6%, and the incidence of skip metastasis (right posterior paratracheal LN metastasis without right anterior paratracheal LN metastasis) was 4.3%. Several studies have reported that all patients with right posterior paratracheal LNs metastasis had right anterior paratracheal LNs metastasis,^{2,4} whereas another study showed that the rate of skip metastasis was 27%.⁶ Right posterior paratracheal LNs metastasis in patients with right-sided PTC are not uncommon.

In the present study, we used univariate and multivariate analysis to investigate the relationship between clinicopathologic factors and right posterior paratracheal LN metastasis in patients with right-sided PTC. In univariate analysis, sex, tumor size (>10 mm), ETE, CLN metastasis, and lateral LN metastasis were associated with right posterior paratracheal LN metastasis ($P < .05$). In multivariate analysis, however, only sex, right anterior paratracheal LNs metastasis, and lateral LNs metastasis were independent predictors of right posterior paratracheal LN metastasis in patients with right-sided PTC ($P < .05$). Bae et al¹ reported that CLN metastasis was an independent risk factor for right posterior paratracheal LN metastasis by univariate analysis. Other studies have

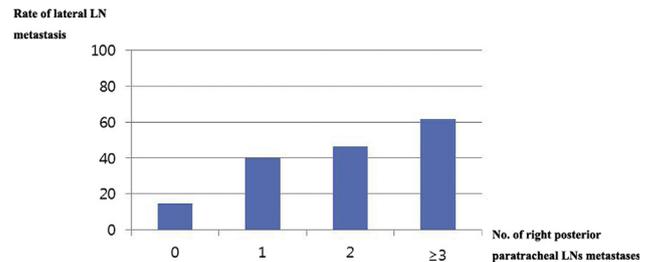


Fig 2. Rate of lateral neck lymph nodes (LNs) metastasis according to the number of right posterior paratracheal LNs metastases. The result was increased according to the number of right posterior paratracheal LNs metastases ($P < .001$, OR 9.461, CI 3.029–29.552).

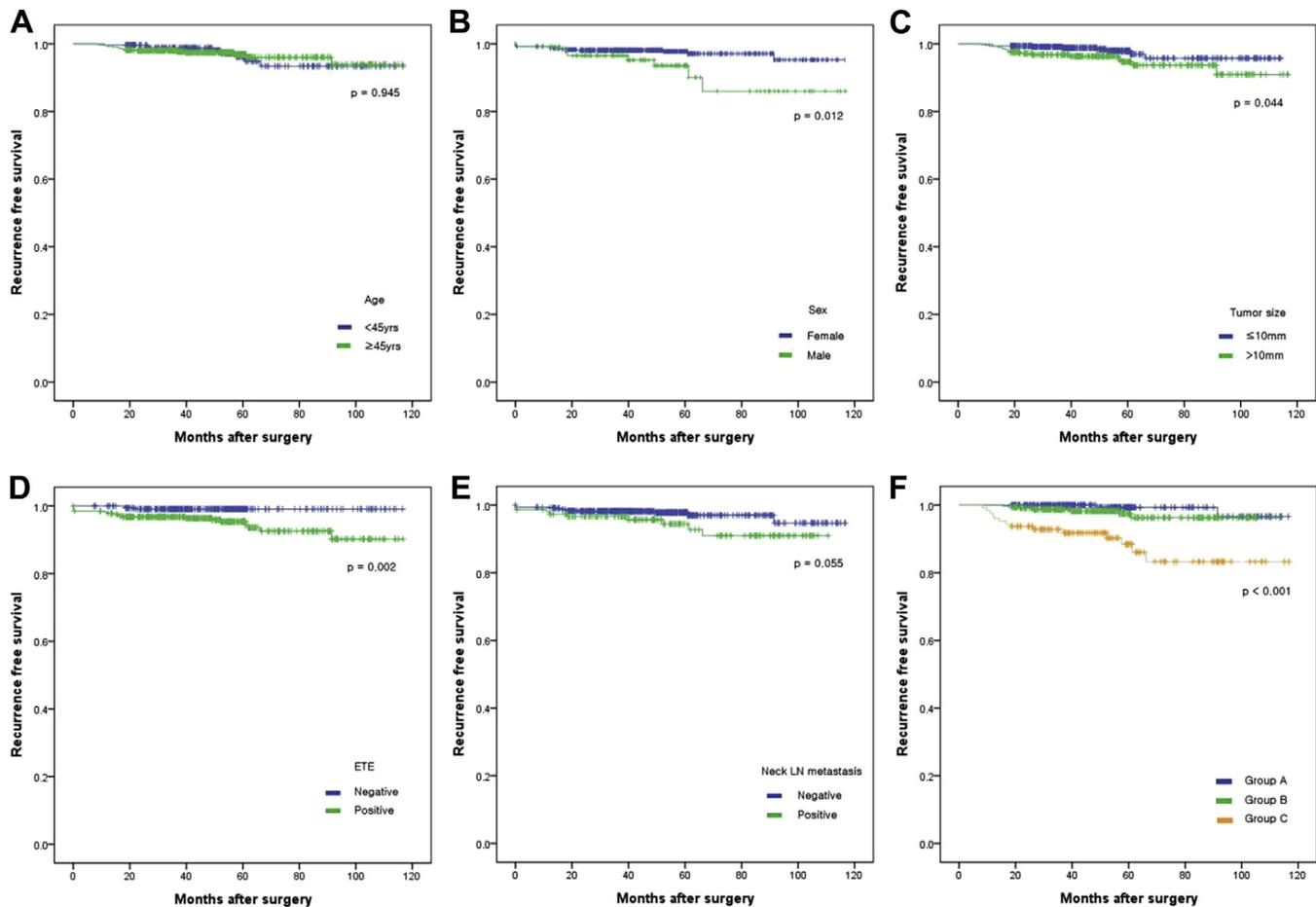


Fig 3. The Kaplan–Meier analysis of the recurrence free survival. (A) Sex, (B) age, (C) tumor size, (D) extrathyroidal extension (ETE), (E) lateral neck lymph nodes (LNs) metastasis, and (F) the state of right anterior and posterior paratracheal LNs metastasis. Male, tumor size (>10 mm), ETE, and the state of right posterior paratracheal LNs metastasis are factors associated with loco-regional recurrence.

demonstrated that lateral LN metastasis was a dependent predictor of right posterior paratracheal LNs metastasis.^{4,12}

Fifty-six (37.1%) of the 151 patients who underwent lateral cervical neck dissection had nodal metastasis in the right posterior paratracheal LNs. Seventy-one (11.6%) of the 612 patients who did not undergo lateral cervical LN dissection had nodal metastasis in this area. This difference was statistically significant on both univariate and multivariate analysis, and we found a statistically significant correlation ($P < .001$). Furthermore, the rate of lateral cervical LNs metastasis increased according to the number of right posterior paratracheal LNs metastases (Fig 2). These findings suggest that the right posterior paratracheal LNs should be removed during CLN dissection in patients with right-sided PTC with lateral cervical LN metastasis.

Although the prognosis of most patients with PTC is good, postoperative loco-regional recurrence is a stressful event for both patients and surgeons because of the difficulty of reoperation and the high incidence of complications such as recurrent laryngeal nerve injury and hypoparathyroidism with a reoperation.¹³ Therefore, recurrence is an important factor affecting quality of life in patients with PTC with a high survival rate. In the present study, male sex, tumor size, ETE, and right posterior paratracheal LNs metastasis were the factors affecting loco-regional recurrence. The first echelon of nodal metastases of the thyroid is the CLNs, with extension to the lateral cervical LNs.^{14,15} A positive node in the CLNs may hint at the probability of lateral cervical LN metastasis. Several studies have reported that lateral cervical LN metastasis is

associated with high rates of loco-regional recurrence^{16–18}; however, in our study, lateral cervical LN metastasis showed an association of borderline significance ($P = .055$) with loco-regional recurrence. Extranodal extension and number and/or ratio of metastatic LNs have been found to be factors affecting recurrence in previous studies,^{19–21} but we did not analyze these factors in the present study. Several previous studies have evaluated the incidence and clinic-pathologic features of right posterior paratracheal LNs metastasis, but no studies have evaluated the predictive importance of right posterior paratracheal LNs metastasis. Therefore, this study is the first to demonstrate that posterior paratracheal LNs metastasis is a predictor factor of loco-regional recurrence in patients with right-sided PTC ($P < .001$). Additional study is needed to determine the prognostic importance of the number and ratio of right posterior paratracheal lymph node metastases. And, in patients with right posterior paratracheal LNs metastasis, more careful postoperative follow-up is required.

Male sex, right anterior paratracheal LNs metastasis, and lateral LNs metastasis were statistically significant, independent predictors by multivariate analysis of right posterior paratracheal LNs metastasis in patients with right-sided PTC. The loco-regional recurrence rate was greater in the groups of patients who were male and those with larger tumor size, ETE, and right posterior paratracheal LNs metastasis. These results suggest that the right posterior paratracheal LNs metastasis is one of independent predictive factors of loco-regional recurrence, and these LNs should be completely removed during right CLN dissection in patients

with right-sided PTC with central and/or lateral cervical LN metastasis.

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Conflict of interest/Disclosure

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