

Predictive factors of central lymph node metastasis in papillary thyroid carcinoma

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Purpose: The aim of this study was to evaluate the correlation between central lymph node (CLN) metastasis and clinicopathologic characteristics of papillary thyroid cancer (PTC). In addition, we investigated the incidence and risk factors for contralateral CLN metastasis in unilateral PTC. This study suggests the appropriate surgical extent for CLN dissection.

Methods: A prospective study of 500 patients with PTC who underwent total thyroidectomy and prophylactic bilateral CLN dissection was conducted.

Results: Of 500 patients, 255 had CLN metastases. The rate of CLN metastasis was considerably higher in cases of younger patients (<45 years old) ($P < 0.001$; odds ratio [OR], 2.357) and of a maximal tumor size greater than 1 cm ($P < 0.001$; OR, 3.165). Ipsilateral CLN metastasis was detected in 83.1% of cases (133/160) of unilateral PTC, only contralateral CLN metastases in 3.7% of cases (6/160), and bilateral CLN metastases in 13.1% of cases (21/160). The rate of contralateral CLN metastasis was considerably higher in cases of PTC with a large tumor size (≥ 1 cm) ($P = 0.019$; OR, 4.440) and with ipsilateral CLN metastasis ($P = 0.047$; OR, 2.613).

Conclusion: Younger age (<45 years old) and maximal tumor size greater than 1 cm were independent risk factors for CLN metastasis. Maximal tumor size greater than 1 cm and presence of ipsilateral CLN macrometastasis were independent risk factors for contralateral CLN metastasis. Therefore, both CLN dissections should be considered for unilateral PTC with a maximal tumor size greater than 1 cm or presence of ipsilateral CLN macrometastasis.

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Key Words: Lymph node, Metastasis, Papillary thyroid cancer

INTRODUCTION

Thyroid carcinoma accounts for approximately 1% of all tumors and one third of all head and neck tumors. Papillary thyroid carcinoma (PTC) makes up 85% to 90% of all thyroid carcinoma cases, with a reported 10-year survival rate of more than 90% [1]. Although PTC has a good prognosis, central lymph node (CLN) metastases are common. The occurrence of CLN metastasis ranges from 40% to 90% of PTC cases [2]. CLN metastasis is a well-known independent risk factor in local recurrence [3-5] but has little adverse effect on survival [5,6].

However, this conventional knowledge has become debated due to a large, recent case-based study which showed an increased mortality rate in patients with regional lymph node metastasis [1].

Prophylactic central lymph node dissection (CLND) is an accepted procedure for patients with PTC. However, CLND might increase the rates of hypoparathyroidism and vocal cord palsy, especially when bilateral CLND is performed [7]. Thus, identification of predictive factors for CLN metastasis might prevent unnecessary contralateral CLND.

Recently, PTC has been diagnosed at earlier stages through

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screening. When prophylactic CLND is performed, many CLN metastases are microscopic deposits [8].

In this study, we examine the clinicopathologic characteristics of PTC with CLN metastasis and investigate the incidence and risk factors for contralateral CLN metastasis in unilateral PTC. In addition, we describe the incidence and characteristics of CLN micrometastases and suggest the appropriate surgical extent for CLND.

METHODS

Eligibility

Our prospective study was approved by the Institutional Review Board of Chungnam National University Hospital, and written informed consent was obtained from participants. In 2001 and 2012, 500 patients with PTC who underwent a total thyroidectomy with bilateral prophylactic CLND were enrolled in this prospective nonrandomized study. Patients with clinically node-negative necks were evaluated preoperatively through neck ultrasonography, fine needle aspiration biopsy, ¹⁸F fluorodeoxyglucose (¹⁸F-FDG) PET/CT, and physical examination. All patients were clinically node negative. Being clinically node-negative was defined as having no signs of enlarged lymph nodes (LN) during preoperative ultrasonography and no glucose uptake in LN during preoperative ¹⁸F-FDG PET/CT.

Surgical procedure

All patients underwent total thyroidectomy and prophylactic bilateral CLND. First, the entirety of both lobes of the thyroid gland was removed, and then bilateral CLND was performed. CLNs are group VI LNs that surround both lobes of the thyroid and include the pretracheal, paratracheal, and prelaryngeal LNs within an area bordered laterally by the carotid sheath, at the top by the hyoid bone, at the bottom by the sternal notch, and dorsally by the prevertebral fascia. The thymus was preserved through separation from the CLNs, and the parathyroids and recurrent laryngeal nerves were also identified and preserved. Parathyroid glands that could not be preserved *in situ* were autotransplanted into the ipsilateral sternocleidomastoid muscle. At the end of the operation, the surgeon cut separately into the pretracheal nodes (immediately anterior to the trachea) and the paratracheal nodes (adjacent to the trachea on either side), categorized as described above, and sent them to the pathology department for examination. In unilateral thyroid cancer, ipsilateral CLNs are pretracheal and ipsilateral paratracheal LNs, while contralateral CLNs are only contralateral paratracheal LNs.

Statistical analysis

Statistical analysis was performed using SPSS ver. 12.0 (SPSS Inc., Chicago, IL, USA). Pearson chi-square or Fisher exact test

for categorical variables was used in the univariate analyses of the clinical characteristics. Variables with a P-value of less than 0.05 in the univariate analysis were included in multivariate logistic regression analysis.

RESULTS

The clinicopathologic characteristics are presented in Table 1. Of the 500 patients, 255 had metastatic CLNs. Univariate analysis suggested that younger age (<45 years old), male sex, a large tumor size (≥ 1 cm), bilateral multiple nodules, and the presence of capsular invasion or extrathyroidal extension were significant factors in CLN metastasis (Table 1). With CLNs removed in the multivariate analysis, the rate of CLN metastasis was considerably higher in the cases of younger patients (<45 years old) ($P < 0.001$; odds ratio [OR], 2.357) and large tumor size (≥ 1 cm) ($P < 0.001$; OR, 3.165) (Table 2).

Table 1. Correlation between clinicopathological characteristics and central lymph node metastasis in papillary thyroid cancer

Characteristic	No. of patients (n = 500)	Positive CLN	P-value ^{a)}
Age (yr)			0.001
<45	160	109 (68)	
≥ 45	340	146 (43)	
Sex			0.038
Male	58	37 (64)	
Female	442	218 (49)	
Tumor size (cm)			0.004
≤ 0.5	149	39 (26)	
$>0.5, <1$	197	93 (47)	
≥ 1	154	123 (80)	
Bilaterality			0.008
Unilateral	341	160 (47)	
Bilateral	159	90 (57)	
Multiplicity			0.005
Solitary	288	130 (45)	
Multiple	212	125 (59)	
Capsule invasion			0.004
Yes	314	192 (61)	
No	186	63 (34)	
Extrathyroidal extension			0.002
Yes	248	153 (62)	
No	252	102 (40)	
Lymphovascular invasion			0.005
Yes	401	243 (61)	
No	99	12 (12)	
No. of CLN removed	9.05 \pm 7.03	10.21 \pm 6.25	0.580
No. of CLN metastasis	-	1.52 \pm 2.76	

Values are presented as number (%) or mean \pm standard deviation. CLN, central lymph node.

^{a)}Pearson chi-square test for categorical variables was used for univariate analyses of the clinical characteristics.

The trend of CLN metastasis in unilateral PTC patients is depicted in Fig. 1. Of 341 patients with unilateral PTC, 160 had CLN metastases. We excluded isthmic PTC in patients with unilateral PTC analysis.

Ipsilateral CLN metastasis was detected in 83.1% of cases (133/160) of CLN metastases in patients with unilateral PTC, only contralateral CLN metastases in 3.7% (6/160), and bilateral CLN metastases in 13.1% (21/160). The clinicopathologic characteristics of patients with contralateral CLN metastases are shown in Table 3. In the univariate analysis, large tumor size

(≥1 cm), lymphovascular invasion, and positive ipsilateral CLNs were significant predictors of contralateral CLN metastases in unilateral PTC (P < 0.05) (Table 3). In the multivariate analysis, the rate of contralateral CLN metastasis was considerably higher in the cases of PTC with a large tumor size (≥1 cm) (P = 0.019; OR, 4.440) or ipsilateral CLN metastasis (P = 0.047; OR, 2.613) (Table 4).

Permanent hypocalcemia occurred in 22 patients (4.4%), while permanent recurrent laryngeal nerve paralysis did not occur in the present study (Table 5).

Table 2. Correlation between clinicopathologic characteristics and central lymph node metastasis in papillary thyroid cancer by multivariate logistic regression analysis

Variable	$\beta \pm SE$	P-value	Odds ratio (95% CI)
Age < 45 yr	0.857 ± 0.235	<0.001	2.357 (1.488–3.735)
Male gender	0.496 ± 0.337	0.153	1.612 (0.837–3.104)
Tumor size ≥ 1 cm	1.801 ± 0.303	<0.001	3.165 (1.697–7.299)
Bilateral tumor	0.463 ± 0.362	0.957	1.013 (0.781–3.229)
Capsular invasion	0.538 ± 0.343	0.116	1.712 (0.875–3.352)
Lymphovascular invasion	0.847 ± 0.368	0.086	1.312 (0.373–2.699)
Constant	-1.003 ± 0.451	-	-

SE, standard error; CI, confidence interval.

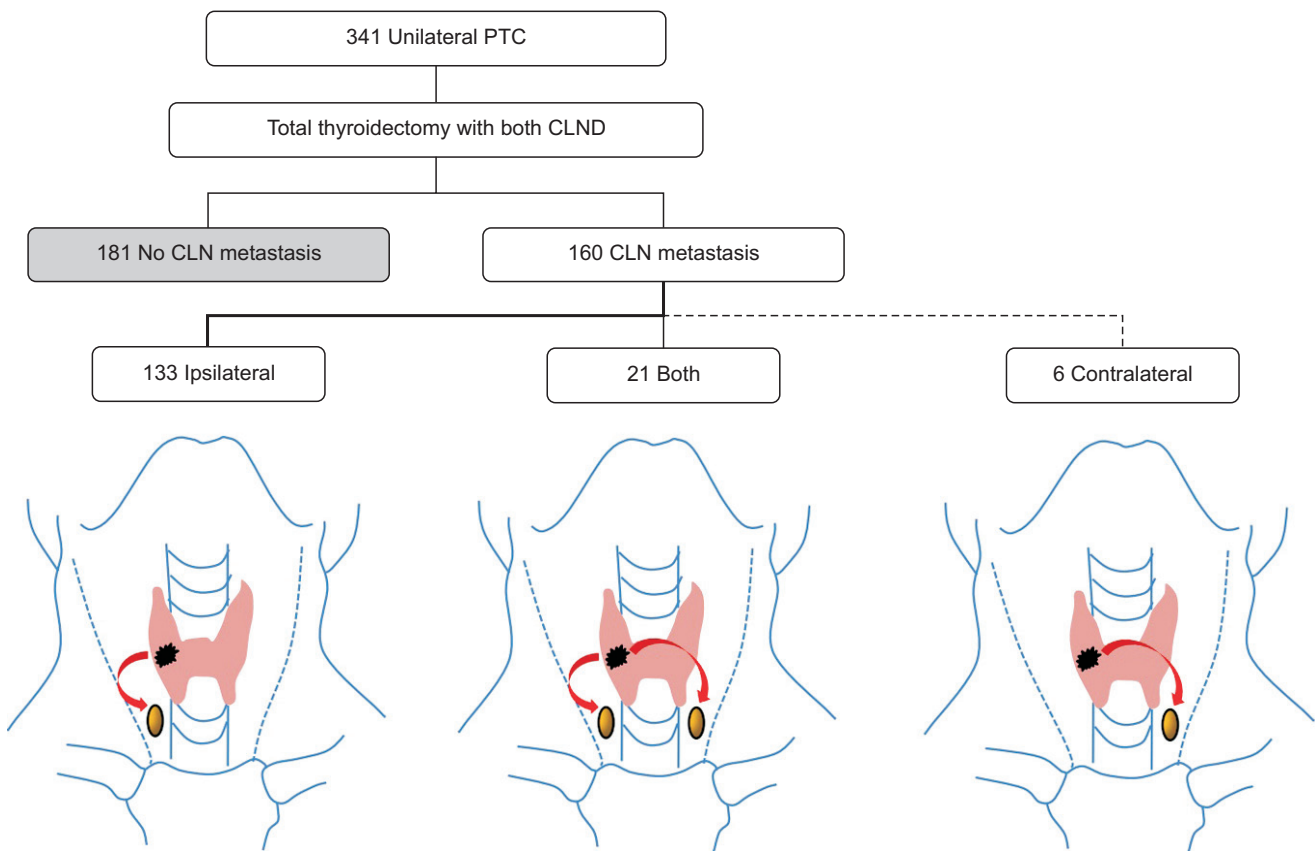


Fig. 1. Trend of central lymph node (CLN) metastasis in unilateral papillary thyroid cancer (PTC). CLND, central lymph node dissection.

Table 3. Correlation between clinicopathological characteristics and contralateral central lymph node metastasis in unilateral papillary thyroid cancer

Variable	Contralateral CLN metastasis (n = 27)	P-value ^{a)}
Age (yr)		0.086
<45	12/102	
≥45	15/239	
Sex		0.067
Male	6/39	
Female	21/302	
Tumor size (cm)		<0.001
≤0.5	5/122	
>0.5, <1	9/133	
≥1cm	13/86	
Multiplicity		0.447
Solitary	22/279	
Multiple	5/62	
Capsule invasion		0.377
Yes	17/187	
No	10/154	
Extrathyroidal extension		0.495
Yes	13/143	
No	14/198	
Lymphovascular invasion		0.003
Yes	27/262	
No	0/79	
Ipsilateral central LN (+)		<0.001
Yes	21/154	
No	6/187	

CLN, central lymph node; LN, lymph node.

^{a)}Pearson chi-square test or Fisher exact test for categorical variables was used for univariate analyses.

Table 4. Correlation between clinicopathologic characteristics and contralateral central lymph node metastasis in unilateral papillary thyroid cancer by multivariate logistic regression analysis

Variable	$\beta \pm SE$	P-value	Odds ratio (95% CI)
Tumor size ≥ 1 cm	1.491 ± 0.637	0.019	4.440 (1.273–15.486)
Lymphovascular invasion	1.719 ± 0.000	0.066	1.312 (0.373–2.699)
Ipsilateral LN (+)	0.960 ± 0.505	0.047	2.613 (1.972–5.025)
Constant	19.217 ± 0.642	-	-

SE, standard error; CI, confidence interval.

Eighty-nine patients had CLN micrometastases (Table 6). The rate of CLN micrometastases was higher in cases with a maximal tumor size of less than 1 cm ($P = 0.002$). All the CLN micrometastases occurred on the ipsilateral side of the tumor.

Table 5. Complications (n = 400)

Complication	No. (%)
Hypocalcemia	
Transient	212 (42.4)
Permanent	22 (4.4)
Hoarseness	
Transient	31 (6.2)
Permanent	0 (0)
Chylous fistula	3 (0.6)

Table 6. Characteristics of subgroups of nodal involvement in papillary thyroid carcinoma

Variable	Microscopic metastases (n = 89)	Macroscopic metastases (n = 166)	P-value ^{a)}
Age (yr)			0.109
<45	32 (36)	77 (46)	
≥45	57 (64)	89 (54)	
Sex			0.475
Male	11 (12)	26 (16)	
Female	78 (88)	140 (84)	
Maximal tumor size (cm)			0.002
≤0.5	20 (23)	19 (11)	
>0.5, <1	39 (44)	55 (33)	
≥1	30 (33)	92 (56)	
Bilaterality			0.302
Unilateral	61 (69)	103 (62)	
Bilateral	28 (31)	63 (38)	
Multiplicity			0.797
Solitary	46 (52)	83 (50)	
Multiple	43 (48)	83 (50)	
Capsule invasion			0.470
Yes	65 (73)	128 (77)	
No	24 (27)	38 (23)	
Extrathyroidal extension			0.070
Yes	47 (53)	107 (64)	
No	42 (47)	59 (36)	
Lymphovascular invasion			0.342
Yes	83 (93)	159 (96)	
No	6 (7)	7 (4)	
Contralateral central LN (+)			<0.001
Yes	0 (0)	27 (17)	
No	89 (100)	139 (83)	

Values are presented as number (%).

LN, lymph node.

^{a)}Pearson chi-square test for categorical variables was used for univariate analyses of the clinical characteristics.

DISCUSSION

PTC responds relatively well to surgery and has a good prognosis. However, PTC might recur if the first operation is conducted improperly. A standard treatment for PTC has

not been established. A growing number of studies present prophylactic CLND in synchronization, and some authors even consider CLNs as important as the primary tumor [9]. Therapeutic CLND should be performed on patients with PTC who have preoperative clinical LN metastasis, despite the controversy over clinical N0 (cN0) PTC patients [7,10,11]. Most studies agree that CLNs are involved most frequently in PTC with LN metastasis. The LNs in the central group are most commonly involved in metastases, so there might be a significant risk of recurrence in the central group [12,13]. In addition, reoperation is relatively difficult and complicated in patients who develop loco-regional recurrence in the central group [14,15]. Several studies suggest that prophylactic CLND should not be performed routinely for the majority of cN0 PTC patients, even though a greater incidence of subclinical LN metastasis is expected [16]. Performing CLND has significant associated morbidities, such as recurrent laryngeal nerve injury and hypoparathyroidism. Therefore, it is important to determine the surgical extent of prophylactic CLND in the initial operation for patients with PTC. Recent studies on CLND report transient vocal cord palsy in 3% to 6% of cases and permanent hypoparathyroidism in 3% to 4% of cases [17-21]. In this study, half the patients developed temporary hypoparathyroidism, and 4% continued to experience symptoms for more than 6 months after surgery. These results are similar to those in previous research [7,22]. Permanent recurrent laryngeal nerve paralysis did not occur in the present study. Careful preoperative nodal evaluation for metastasis should be done in order to avoid unnecessary CLND for pN0 patients. However, CLNs are usually small and difficult to identify with ultrasound. Recent studies have shown that the sensitivity in identifying CLN metastases using ultrasonography is 40% to 60% [23,24].

Various predictive factors and staging systems have been used to determine PTC prognosis. Age, gender, tumor size, lymphovascular invasion, extrathyroidal extension, and LN metastasis are generally accepted factors in survival and local recurrence. LN metastases are an independent risk factor for loco-regional recurrence and distant metastasis [25]. Evidence from large population-based studies shows that patients with regional LN metastases have poor prognosis and higher mortality [1,17]. Numerous studies have found CLN metastases in 50% to 70% of PTC patients [13,20,26,27]. In the present study, 51% of PTC patients (255/500) had CLN metastases. Most studies agree that ipsilateral CLN metastases are frequently involved in the LN metastasis of PTC [8,13,28]. Prophylactic CLND ipsilateral to the tumor associated with

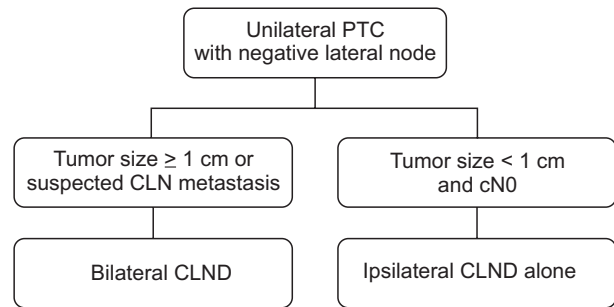


Fig. 2. Suggested scheme of decision making in unilateral papillary thyroid cancer (PTC). The ipsilateral central lymph node (CLN) metastasis could be evaluated by clinical examination or intraoperative pathology. CLND, CLN dissection.

total thyroidectomy could be an effective strategy for reducing the rates of permanent hypoparathyroidism and hoarseness. Generally, for unilateral PTC, the rate of metastasis to contralateral CLN was very low, and the rate of disease-free survival did not improve after bilateral CLND, indicating that contralateral CLND is unnecessary [12,29]. Among the unilateral PTC patients with CLN metastases participating in the present study, contralateral CLN metastasis occurred mostly in the patients who had ipsilateral CLN macrometastasis or a maximal tumor size greater than 1 cm (Tables 4, 6).

We recommend that total thyroidectomy with simultaneous completion of contralateral CLND be performed in the presence of ipsilateral CLN macrometastasis in intraoperative frozen-section pathology. This approach could limit unnecessary contralateral CLND for node-negative patients based on intraoperative pathological findings. According to the results of this study, both prophylactic CLND should be considered for unilateral PTC with a large tumor size (≥ 1 cm) or the presence of ipsilateral CLN macrometastasis. In contrast, prophylactic ipsilateral CLND has a satisfactory surgical extent for the initial operation in patients with PTC who have a small tumor and no ipsilateral CLN macrometastasis (Fig. 2).

There were no local recurrences during the follow-up period for this study. Local recurrence and disease-free survival could not be described because of the short follow-up duration. A long-term follow-up of the present study is necessary to evaluate local recurrence and disease-free survival.

CONFLICTS OF INTEREST

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

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