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Lateral Lymph Node Metastasis Prediction in Papillary Thyroid Cancer Patients with Suspicious Preoperative Imaging Findings

Han Shin Lee, Eun Jung Jung[1], Ju Yeon Kim, Seung Jin Kwag, Taejin Park[1], Sang Ho Jeong[1], Chi Young Jeong, Young Tae Ju, Young Joon Lee, Soon Chan Hong, Sang Kyung Choi, Woo Song Ha

Department of Surgery, Gyeongsang National University Hospital, Gyeongsang National University School of Medicine, Jinju, [1]Department of Surgery, Gyeongsang National University Changwon Hospital, Gyeongsang National University School of Medicine, Changwon, Korea

Purpose: Lateral lymph node metastasis of papillary thyroid cancer (PTC) is indicative of tumor aggressiveness and can determine treatment strategies. However, the role of prophylactic lateral lymph node dissection in the management of PTC is unclear. This study evaluated factors predictive of lateral lymph node metastasis in patients with suspicious lymph node enlargement in preoperative imaging.

Methods: This retrospective study included 728 patients with newly diagnosed PTC who underwent therapeutic surgery. Clinicopathologic results were reviewed, and factors predictive of lateral lymph node metastasis were analyzed.

Results: Of the 242 patients with lymph node metastasis, 50 had lateral lymph node metastasis. Lateral lymph node metastasis was associated with sex, tumor size, preoperative thyroid stimulating hormone (TSH) concentration and presence of central lymph node metastasis. Among patients with suspicious lateral lymph node metastasis by ultrasonography, high TSH level (odds ratio 3.833, P=0.031) and number of metastatic central lymph nodes (odds ratio 3.68, P=0.025) were significantly predictive of lateral lymph node metastasis.

Conclusion: High serum TSH level and central lymph node metastasis were predictive of lateral lymph node metastasis in PTC patients with suspicious preoperative imaging findings. These predictive factors might help reduce unnecessary therapeutic lateral lymph node dissection.

Key Words: Papillary thyroid cancer, Lateral lymph node metastasis, TSH concentration, Ultrasonography

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Correspondence: **Eun Jung Jung**
Department of Surgery, Gyeongsang National University Changwon Hospital, Gyeongsang National University School of Medicine, 11, Samjeongja-ro, Seongsan-gu, Changwon 51472, Korea
Tel: +82-55-214-1000
Fax: +82-55-214-1031
E-mail: drjej@gnu.ac.kr

INTRODUCTION

Papillary thyroid carcinomas (PTCs) generally grow slowly, resulting in a good prognosis; however, PTCs metastasize to regional lymph nodes in 30～80% of patients.(*1*) The lateral lymph node compartment is the second most common region of metastasis, following the central compartment. Metastasis to the lateral compartment is important because it reflects the biologic aggressiveness of the tumor.(*2*)

Indications for lateral node dissection remain unclear because that procedure requires wound extension, which can increases the risk of complications and worsen cosmetic outcomes and patients satisfaction after surgery.

Modified radical neck dissection is the treatment of choice for patients with lateral lymph node metastasis (LNM). The efficacy of prophylactic lateral neck dissection in patients with PTC and clinically negative lateral neck nodes, however, remains undetermined.(*3-5*) Therefore preoperative identification of patients with lateral LNM is important in determining surgical strategies.

The American Thyroid Association (ATA) recommends the routine use of ultrasound (US) to assess the presence or absence of LNM in patients with PTC.(*6*) Sonographic features suggestive of abnormal metastatic lymph nodes include loss of the fatty hilum, a rounded rather than oval shape, hypoechogenicity, cystic change, calcifications, and peripheral vascularity. However, no single feature is adequately sensitive for the detection of lymph nodes with metastatic thyroid cancer.(*7,8*)

Patients with evidently suspicious lateral LNM seen via ultrasonography or physical examination are more likely to have histopathologic lateral LNM. However, some of those patients have no lateral LNM. This study, therefore evaluated the clinicopathologic factors predictive of lateral LNMs in patients with PTC, especially, in patients with suspicious LNM on preoperative ultrasonography.

METHODS

The medical records of all patients who underwent surgery for PTC at a single institution between January 2005 and December 2014 were retrospectively evaluated. Patients with other malignancies or a history of previous thyroidectomy were excluded, as were those treated for hypo- or hyperthyroidism. A review of medical records identified a total of 728 patients with PTC eligible for this study.

Epidemiologic factors and pathologic characteristics after surgery were based on chart review. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared.

Preoperatively, all patients underwent thyroid function tests and ultrasonography to evaluate neck LNM. Some patients suspected of LNM were assessed by ultrasound - guided fine needle aspiration. Patients who had cytologically positive for malignant lymph node cells underwent total thyroidectomy plus unilateral lateral neck dissection. If fine needle aspiration could not be performed or if metastatic cells were absent on cytological analyses, intraoperative frozen section analysis was performed, with the extent of surgery based on the results of these analyses.

Continuous variables were compared using Student's t test or one-way analysis of variance, and categorical variables were compared using Chi-squared tests. Logistic regression analysis was performed to determine factors significantly associated with lateral LNM. All statistical analyses were performed using SPSS ver. 15.0 (SPSS Inc., Chicago, IL, USA), and P values <0.05 were considered statistically significant.

RESULTS

The clinical and histopathologic features of the 728 included patients are listed in Table 1. Of these, 463 (63.6%) patients had PTCs $\leq$1 cm in diameter. Mean patients age was 48.73 years (range, 15 to 80 years). Capsular invasion was detected in 338 (46.4%) patients, and thyroiditis in 87 (12.0%) patients. Preoperative serum TSH concentration ranged from 0.01 to 13.6 mIU/L. A total of 242 (33.2%) patients had LNM, including, 38 with both central and lateral LNM, 192 with central LNM alone, and 12 with lateral LNM alone.

1. Factors predictive of LNM

LNM was significantly associated with male sex, younger age, large tumor size, capsular invasion and multiplicity, but not with TSH concentration or BMI (Table 2).

Lateral LNM was identified in 50 PTC patients and was more frequent in male than female patients. Mean tumor size was significantly larger (1.06 ± 0.73 cm vs. 1.30 ± 0.95 cm, P=0.031) and mean preoperative TSH concentration significantly higher (1.93 ± 1.41 mIU/L vs. 2.40 ± 1.62 mIU/L, P=0.027) in patients with than without lateral LNM. Patients with central LNM tended to be positive for lateral LNM. The numbers of metastatic central lymph nodes was significantly greater in patients with than without lateral LNM (0.73 ± 1.58 vs. 2.66 ± 2.65, $P<0.001$).

Table 1. The clinicopathologic features of patients with papillary thyroid cancer

	Total patients (N=728)
Age (mean±SD, year)	15~80 (48.73±12.60)
Sex	
Male:Female (%)	114 : 614 (15.7:84.3%)
Operation methods	
Less total thyroidectomy	209 (28.7%)
Total thyroidectomy	519 (71.3%)
Tumor size (mean±SD, cm)	0.1~5.0 (1.08±0.75)
Size≤1 cm	463 (63.6%)
LN metastasis status	
N0	486 (66.8%)
N1	242 (33.2%)
Subgroup (Central LNM:Lateral LNM)	
Positive:negative	192 (26.4%)
Positive:positive	38 (5.2%)
Negative:positive	12 (1.6%)
Capsular invasion	338 (46.4%)
Multiplicity	216 (29.7%)
Thyroiditis	87 (12.0%)
Preoperation TSH level (mean±SD, mIU/L)	0.01~13.60 (1.97±1.43)
Preoperative Tg Ag level (mean±SD, ng/mL)	0.01~98.59 (53.02±42.02)
BMI (kg/m^2)	14.01~40.47 (24.63±3.57)
Underweight (<18.5)	14 (1.9%)
Normal (18.5~25)	418 (57.4%)
Over weight (25~30)	243 (33.4%)
Obese (≥30)	53 (7.3%)

N = number; SD = standard deviation; LN = lymph node; LNM = lymph node metastasis; TSH = thyroid stimulating hormone; Tg = Thyroglobulin; BMI = body mass index.

Table 2. Clinicopathological characteristics according to lymph node metastasis status

	LN metastasis status			Lateral LN metastasis status		
	Negative (N=486)	Positive (N=242)	P value	Negative (N=678)	Positive (N=50)	P value
Sex (%)			0.018			0.008
Male	65 (13.4)	49 (20.2)		99 (14.6)	15 (30.0)	
Female	421 (86.6)	193 (79.8)		579 (85.4)	35 (70.0)	
Age	49.51±12.26	47.14±13.14	0.017	48.94±12.56	45.89±12.89	0.098
Tumor size (mean±SD, cm)	0.97±0.67	1.31±0.85	<0.001	1.06±0.73	1.30±0.95	0.031
Capsular invasion (%)	201 (41.4)	137 (56.6)	<0.001	312 (46.0)	26 (52.0)	0.464
Multiplicity (%)	118 (24.3)	98 (40.5)	<0.001	197 (29.1)	19 (38.0)	0.200
Thyroiditis (%)	53 (11.0)	34 (14.0)	0.228	83 (12.3)	4 (8.0)	0.499
Preoperation TSH level (mean±SD, mIU/L)	1.93±0.67	2.05±1.43	0.293	1.93±1.41	2.40±1.62	0.027
Preoperation Tg Ag level (mean±SD, ng/mL)	42.78±35.21	72.56±47.94	0.012	51.10±40.30	75.66±56.63	0.188
BMI (mean±SD, kg/m^2)	24.62±3.59	24.65±3.54	0.895	24.62±3.55	24.75±3.93	0.809
Central LN metastasis				193 (28.5)	38 (76.0)	<0.001
Metastatic central LN number (mean±SD)				0.73±1.58	2.66±2.65	<0.001

LN = lymph node; N = number; SD = standard deviation; BMI = body mass index.

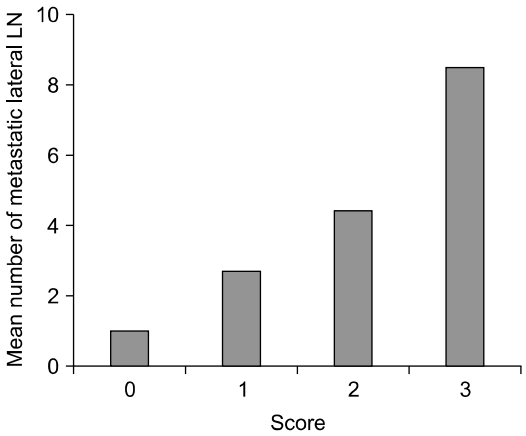
2. Factors predictive factors of lateral LNM in patients suspicious for lateral LNM on ultrasonography

Ultrasound identified 72 patients suspicious for lateral LNM, with histopathologic examination showing that 50 (69.4%) were positive for lateral LNM. Among these 72 patients underlying thyroiditis, preoperative serum TSH concentration and number of metastatic central lymph

Table 3. Predictive factors of lateral LNM of the patients with ultrasonography-detectable suspicious lateral LNM

	Lateral LN metastasis status			Logistic regression analysis	
	Negative (N=22)	Positive (N=50)	P value	OR (95%CI)	P value
Sex (M:F)	5:17 (22.7%:77.3%)	15:35 (30.0%:70.0%)	0.582		
Multiplicity	7 (31.8%)	19 (38.0%)	0.791		
Capsular invasion	12 (54.5%)	26 (52.0%)	1.000		
PTMC (≤1 cm)	13 (59.1%)	25 (50.0%)	0.610		
Thyroiditis	7 (31.8%)	4 (8.0%)	0.028	4.312 (1.08~17.27)	0.039
Age (year)	49.86±13.07	45.88±12.89	0.233		
Size (cm)	1.10±0.60	1.30±0.95	0.366		
BMI (kg/m^2)	24.10±3.18	24.75±3.93	0.501		
TSH (mIU/L)	1.47±0.95	2.40±1.62	0.003		
TSH>1.97 mIU/L	4 (14.8%)	18 (40.0%)	0.034	3.8333 (1.13~12.96)	0.031
Metastatic central LN number	1.23±1.95	2.66±2.65	0.013		
Central LN meta ≥2	5 (22.7%)	26 (52.0%)	0.037	3.683 (1.18~11.53)	0.025

LN = lymph node; N = number; OR = odds ratio; PTMC = Papillary thyroid microcarcinoma; BMI = body mass index; TSH = thyroid stimulating hormone.



Parameters		Score
Thyroiditis	Absent	1
	Present	0
TSH level (mIU/L)	>1.97	1
	≤1.97	0
Number of Central LN metastasis	≥2	1
	<2	0

Fig. 1. Numbers of metastatic lateral lymph nodes according to risk score. The table shows the components of the scoring system and the mean numbers of lateral lymph node metastasis is shown in the right panel.

node were significantly associated with lateral LNM positivity. Using a TSH cutoff of 1.97 mIU/L, the mean concentration in patients with PTC, high TSH level was significantly predictive of lateral LNM (odds ratio [OR] 3.833, 95% confidence interval [CI], 1.13~12.96; P=0.031). In addition, the presence of two or more metastatic central lymph node was independently predictive of lateral LNM factor (Table 3).

Based on these results, we conducted a scoring system to estimate the likelihood of lateral LNM in suspicious patients. The score ranged from 0 to 3. There was a correlation between the score and mean number of metastatic lateral LN (Fig. 1).

The mean follow-up duration in the 72 patients suspicious for lateral LNM was 43.53 months (range 6~108 months). During this, time, 10 patients had recurrent diseases, 2 of the 22 (9.1%) negative for lateral LNM and 8 of the 50 (16.0%) positive for lateral LNM, a difference that was not statistically significant.

DISCUSSION

The indications for prophylactic lateral node dissection in PTC patients without clinically apparent LNM remain unclear. Lateral LNMs occur frequently in patients with PTC, but the preoperative detection of LNM including greater accuracy and simplicity and reduced invasiveness, as well as facilitating additional examinations such as

ultrasound-guided biopsy or aspiration.(*4,5,9-11*) Of the 728 patients included in this study, only 72 (9.9%) were suspected of lateral LNM on preoperative ultrasonogrphy.

Traditionally, LNM of PTC patients have been associated with an increased risk of recurrence and lateral LNM have reported as a prognostic factor.(*2*) Although most lymph node metastases are within the central neck compartment, approximately 15% occur in the lateral neck and can be detected by ultrasonography.(*12*) This method has advantages compared with CT and MRI in the preoperative predictive of lateral LNM include male gender, age ≥55 years, massive extrathyroidal extension, tumor size ≥3 cm, histologic features, and tumor location.(*13,14*)

In this retrospective study, the incidence of lateral LNM was 6.8% and the incidence of skip metastasis was 1.6%. Univariate analysis showed that lateral LNM was associated with male gender, large tumor size, high preoperative TSH concentration and presence of central LNM. In patients suspected of lateral LNM on ultrasound, the presence of thyroiditis, preoperatively high TSH concentration and central LNM were predictive of lateral LNM.

Cervical LNM occurs first in the nodes of the central compartment and later in the lateral compartment. Skip metastasis, defined as metastasis to the lateral but not the central compartment, is rare.(*15-18*) Several studies reported that central LNM is important indicator of lateral LNM.(*19-21*) The sensitivity and specificity of central node involvement in predicting lateral LNM were reported to be 85.9% and, 61.4%, respectively, with the presence of two or more positive central nodes associated with a high rate of lateral LNM.(*21*) Similarly, a study of 141 patients with PTMC found that the presence of two or more positive central lymph nodes was predictive of lateral LNM and could help determine the type of surgical intervention needed.(*22*) The specimens dissected from the central LN could be analyzed node metastasis. Therefore, we believed it will be helpful for surgeons in deciding whether further treatment for the lateral compartment is necessary if the number of positive central lymph nodes could be analyzed by intraoperative frozen section with accurate diagnosis.

TSH is involved in the regulation of thyroid function such as secretion of thyroid hormones, maintenance of thyroid-specific gene expression, and gland growth. Even within a normal range, high serum TSH concentration has been associated with the occurrence and extension of PTC.(*22-26*) In recent study, preoperative TSH levels were found to be significantly higher in patients with than without extrathyroidal extension (P=0.002) and in those with than without lateral LNM (P=0.007).(*27*) However, there was no significant difference in mean TSH level in relation to total and central lymph node metastasis. Similarly, in our study, high preoperative TSH was significantly associated with lateral LNM. The effect of TSH in the tumorigenesis and progression on thyroid cancer may differ between studies. In fact, TSH was not versatilely involved in the de novo oncogenesis of PTC.(*28,29*) However, several studies reported that TSH level was associated with high risk-features including extrathyroidal extension and higher TNM stage.(*27*) These findings indicate that serum TSH concentration might be adjunct biochemical product.

Interestingly, the occurrence of thyroiditis was negatively predictive of lateral LNM. Similarly, more lymph nodes were resected in PTC patients with than without thyroiditis, but the proportion of metastatic lymph nodes was lower in those with thyroiditis.(*30*) In these patients, reactive lymphadenitis may have been misdiagnosed as metastatic lymphadenopathy.

Our study carries several limitations. Due to its retrospective nature, there may have been a selection bias. And our data is based on a single institution's experience necessitate the prospective and multi-institutional validation of the prediction model. In addition, insufficient follow-up duration prevented a determination of effect of lateral LNM on survival according to the presence of lateral LNM in patients with suspicious LNM.

CONCLUSION

In our study, high TSH concentration and central LNM were found to be factors predictive of lateral LNM in PTC patients with suspicious preoperative imaging findings.

Therefore, we suggested that paying more attention to these factors might reduce unnecessary therapeutic lateral

lymph node dissection.

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