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The Efficacy of Lateral Neck Sentinel Lymph Node Biopsy in Papillary Thyroid Carcinoma

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Abstract

Background Although occult lymph node metastasis to the lateral neck compartment is common in papillary thyroid carcinoma, the incidence and patterns of lateral neck node metastasis in papillary carcinoma are not known. We hypothesized that sentinel lymph node biopsy (SLNB) with radioisotope in the detection of occult lateral neck node metastasis would be useful in characterizing metastasis in papillary carcinoma.

Methods Ninety-four patients with papillary thyroid carcinoma were included from June 2009 to March 2010 for lateral neck SLNB. Preoperative lymphoscintigraphy was obtained after intratumoral injection of a ^{99m}Tc-tin colloid under ultrasound guidance. Total thyroidectomy or lobectomy preceded SLN detection to avoid radioactivity interference with the primary tumor, after which SLNB was performed in the lateral neck nodes. In the cases where metastasis was detected in SLNs upon frozen biopsy, an immediate modified radical neck node dissection was performed.

Results A total of 174 SLNs were identified in 60 patients (63.8%). The identification rate of the SLNs with isotope increased with time. Sentinel lymph node metastasis was found in 19 patients (31.7%). This clinically occult metastasis was only related to the total number of metastatic LNs in the central compartment. Patient age, gender, tumor size, location, extent of tumor invasion, multiplicity, and presence of thyroiditis were not related to metastasis in the lateral compartment. Detection of lateral neck SLNs upon biopsy with radioisotope was also feasible in level II and contralateral neck.

Conclusions Sentinel lymph node biopsy is a useful method for evaluating the occult lateral neck lymph node status in patients with papillary thyroid carcinoma, especially in the cases of central neck node metastasis.

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Introduction

Lymph node metastasis is relatively common (up to 70%) in differentiated thyroid carcinoma (DTC) even when tumors are small [1]. There is controversy over whether prophylactic lymph node dissection improves the prognosis and survival of thyroid carcinoma patients [2, 3]. In Europe and United States, prophylactic modified radical neck dissection was not performed routinely because of the role of adjuvant iodine ablation therapy [2, 4, 5]. However, some authors, especially in Japan, have insisted that prophylactic modified radical neck dissection improves prognosis [6–9].

Sentinel lymph node biopsy (SLNB) in thyroid carcinoma was introduced in 1998 [10], and several studies have evaluated the utility of this technique and its reported feasibility in the detection of occult metastasis in thyroid carcinoma patients [11–20]. However, most reports of SLNB in thyroid carcinoma patients are focused on the central neck node. Reports including sentinel lymph node biopsy of the lateral neck node are rare [18].

Although the prognostic significance of lateral neck occult lymph node metastases in thyroid carcinoma patients remains controversial, the identification of these

patients may be helpful in avoiding secondary operation due to recurrence in the lateral compartment. The objective of this study was to determine the usefulness of isotope-guided SLNB in the detection of occult lateral neck node metastasis in patients with papillary thyroid carcinoma.

Patients and methods

Patient selection

A prospective study was conducted in patients with PTC larger than 1 cm and/or suspicious central neck node metastasis in order to evaluate the efficacy of SLNB in the lateral neck compartment (LSLNB). From June 2009 to March 2010, 94 patients with papillary thyroid carcinoma underwent LSLNB in the Department of Surgery at the Samsung Medical Center. All patients underwent an ultrasound with/without CT evaluation of the neck prior to operation. Cases with tumors larger than 1 cm in size or with suspicious central neck node metastasis were included. Patients in whom a fine needle aspiration biopsy (FNAB) had confirmed lateral neck lymph node metastases were excluded from this study. In cases of bilaterally located multifocal tumors, the isotope was injected into the largest tumor.

Procedure

On the day of surgery, patients underwent preoperative lymphoscintigraphy after the intratumoral injection of a ^{99m}Tc-tin colloid in 0.1–0.2 ml saline under ultrasound guidance. Total thyroidectomy or lobectomy with central neck dissection preceded SLN detection to avoid interference by primary tumor radioactivity. After total thyroidectomy or lobectomy, we performed the dissection toward the internal jugular chain beneath the sternocleidomastoid muscle. A hand-held collimated gamma probe was used to scan the lateral compartments (through skin and under the SCM) for "radioactive" lymph nodes. Removed SLNs were also immediately submitted for frozen biopsy. If any of the SLNs were positive for metastasis on the frozen section, modified radical neck dissection (MRND) was performed immediately. In the case of metastasis detection in the lateral neck node after lobectomy with central neck node dissection, we performed complete thyroidectomy for additional radioactive iodine (RAI) therapy.

For statistical analysis, we used SPSS version 17 software (SPSS Inc., Chicago, IL). Univariate analyses for associations between occult LN metastases and several clinicopathologic factors of the primary lesion were performed with Pearson's chi-square test or Fisher's exact test. Statistical significance was defined as $P = 0.05$.

Results

Characteristics of patients

A total of 94 papillary thyroid cancer patients were enrolled for lateral sentinel lymph node biopsy. Median tumor size was 1.36 cm in diameter. In 27 cases, thyroiditis accompanied the tumor. Primary tumor locations, tumor extent, number of tumors, the thyroid procedures performed, and other characteristics of these patients are shown in Table 1. The mean age at diagnosis was 46.8 years (range: 25–78 years). Of the 94 patients enrolled in this study, 22 were men and 72 were women.

Detection of sentinel lymph nodes in the lateral neck compartment

Sentinel lymph nodes were identified in 60 of the 94 patients (63.8%). Identification rate of the SLNs detected by radioisotope increased with time; in the first 3 months, the detection rate was 54.3% (19/35), which increased to 66.7% (22/33), and 73.1% (19/26), respectively. The median detected number of SLNs was two (1.0, 4.0; IQR). In younger patients, the detection rate of SLNs was higher than that in older patients ($P = 0.044$). No other factors except age were related to detection of SLNs (Table 1). Nineteen of 60 cases were metastatic SLNs (31.7%), which were related to the number of central LN metastases, especially in the ipsilateral central neck node. Patient age, gender, tumor size, location, extent of tumor invasion, multiplicity, and presence of thyroiditis did not show statistical significance (Table 2). Fourteen patients in whom SLN metastasis was revealed on frozen sections underwent immediate MRND. In another five patients, micrometastases in SLNs were confirmed in the permanent pathologic report. If a patient had micrometastasis in one jugular SLN, the decision was made to follow up without an additional operation for the lateral LNs, because of the small size of the metastasis and the high probability of eradication by radioiodine therapy. Ten patients, including five patients in whom metastases were detected only in the permanent pathology report, had lymphatic metastasis only in the SLN of the lateral neck node.

Result of detection methods: lymphoscintigraphy versus gamma probe

All patients underwent lymphoscintigraphy preoperatively, andi n 76.6% of the study population (72 patients) the lymphoscintigraphy study revealed SLN. Among these patients, 59 (81.9%) showed lateral neck node uptake of the radioisotope, and 32 patients showed uptake in both the central neck node and the lateral neck node. Only 23

Table 1 Characteristics of all patients ($n = 94$)

	Total patients ($n = 96$)	Detection ($n = 60$)	No detection ($n = 34$)	P value‖
Mean age, years (±SD)		44.6 (± 11.1)	49.9 (± 12.4)	0.044*
Gender				
Male/female	20/ 74	11 (18.3)/ 49 (81.7)	9 (26.5)/ 25 (73.5)	0.434†
Size, cm	1.36 (1.00, 1.50; IQR)	1.20 (0.93, 1.48; IQR)	1.25 (1.10, 1.53; IQR)	0.518‡
No. of tumor	1.0 (1.0, 2.0; IQR)	1.0 (1.0, .2.0; IQR)	1.0 (1.0, 2.0; IQR)	0.798‡
Location of tumor				
Upper/mid/lower	23/54/17	18 (30.0)/ 31 (51.7)/ 11 (18.3)	5 (14.7)/ 23 (67.6)/ 6 (17.6)	0.246†
Right/left/both	36/38/20	22 (36.7)/ 26 (43.3)/ 12 (20.0)	14 (41.2)/ 12 (35.3)/ 8 (23.5)	0.757†
Tumor extent				
Confined to thyroid	34 (36.2)	24 (40.0)	10 (29.4)	0.300†
Perithyroid	38 (40.4)	25 (41.7)	13 (38.2)	
Extrathyroid	22 (23.4)	11 (18.3)	11 (32.4)	
Operation type				
Lobectomy + CND	5	2	3	
TT + CND	75	44	31	
TT + MRND	14	14	0	
Presence of thyroiditis	27 (28.7)	18 (30.0)	9 (26.5)	0.815†
Detected number of SLNs	–	2.0 (1.0, 4.0; IQR)	–	
Metastatic CLN no.	2.0 (0.0, 3.0; IQR)	1.0 (1.0, 3.0; IQR)	1.5 (0.0, 4.0; IQR)	0.476‡
Total dissected CLN no.	11.7 (7.0, 15.0; IQR)	11.00 (7.00, 16.00; IQR)	11.00 (6.75, 14.25; IQR)	0.755‡

* Student's t-test

† Pearson's chi-square test

† Mann–Whitney test

‖ P value for detection

patients demonstrated ipsilateral lateral neck node uptake; 2 patients revealed contralateral lateral neck node only, and 2 others showed bilateral lateral neck node uptake (Fig. 1). Without lymphoscintigraphy uptake, SLNs were detected with a gamma probe in 6 patients (Fig. 1).

Distribution of SLNs in the lateral neck compartment (Table 3)

In the lateral neck area, 170 SLNs in 60 patients were located in the ipsilateral lateral neck compartment, and four SLNs in two patients were located in the contralateral level III lateral neck compartment only. The patients with contralateral lateral neck SLNs had no SLNs in the ipsilateral neck area. The most common location of SLNs was level IV. Of eight SLNs in level II, four SLNs in three patients showed micrometastasis.

Analysis of cases with metastatic lateral sentinel lymph nodes (Table 4)

Nodal metastasis to a lateral neck node without any central compartment LN metastasis (skip phenomenon) was observed in 3 cases. Among 14 patients who underwent the MRND, 4 patients showed metastasis only in the SLN. Upon analysis of the relation of metastatic level in SLNs and non-SLNs among the 10 patients who had non-SLN metastasis, no relations to the levels of metastatic SLNs and non-SLNs were noted. There was no metastasis in level V.

Discussion

SLNB for in PTC central compartment

Sentinel lymph node biopsy has achieved consensus as a staging procedure in breast cancer and melanoma patients, but the role of SLNB in thyroid carcinoma is not clear. After its introduction by Kelemen et al. [10] in 1998, many authors have described the usefulness of SLNB in thyroid carcinoma patients [11–20]. However, some authors have said that the clinical utility of SLNB in the management of DTC appears uncertain, because of the lack of significance as a prognostic factor of lymph node dissection in DTC and no definite advantage of SLNB in PTC. Moreover, unlike axillary and groin node dissection, there is no need for an additional incision when performing central neck node

Table 2 Comparison of patients with no metastasis and those with metastasis ($n = 60$)

	Metastasis ($n = 19$)	No metastasis ($n = 41$)	P value
Mean age, years (±SD)	42.37 (± 12.04)	45.63 (± 10.68)	0.319*
Gender, M/F	4 (21.1)/15 (78.9)	7 (17.1)/34 (82.9)	0.730†
Multiplicity	6 (31.6)	15 (36.6)	0.778§
Laterality			
Unilateral/bilateral	14 (73.7)/5 (26.3)	34 (82.9)/7 (17.1)	0.493†
Location of tumor			
Upper/mid/lower	4 (21.1)/12 (63.2)/3 (15.8)	14 (34.1)/19 (46.3)/8 (19.5)	0.500‡
Right/left/both	8 (42.1)/6 (31.6)/5 (26.3)	14 (34.1)/20 (48.8)/7 (17.1)	0.423‡
Number of lesions	1.0 (1.0, 2.0; IQR)	1.0 (1.0, 2.0; IQR)	0.615‡
Tumor size	1.3 (1.2, 1.7; IQR)	1.10 (0.85, 1.40; IQR)	0.079‡
Tumor extent			
Confined to thyroid	4 (21.1)	20 (48.8)	0.108†
Perithyroid	10 (52.6)	15 (36.6)	
Extrathyroid	5 (26.3)	6 (14.6)	
Presence of thyroiditis	4 (21.1)	15 (78.9)	0.375§
Total metastatic LN No.	6.0 (3.0, 11.0; IQR)	0.0 (0.0, 2.0; IQR)	0.000‡
Detected number of SLNs	2.0 (2.0, 4.0; IQR)	2.0 (1.0, 4.0; IQR)	0.474‡
Central LN metastasis/total dissected LN, %	14.3 (6.9, 17.6; IQR)	0.0 (0.0, 8.8; IQR)	0.000‡
Central LN metastasis/total dissected CLN, %	40.0 (20.0, 58.3; IQR)	0.0 (0.0, 11.4; IQR)	0.000‡
Total number of central node metastasis	4.0 (2.0, 7.0; IQR)	0.0 (0.0, 2.0; IQR)	0.000‡
Ipsilateral central node metastasis	3.0 (1.0, 5.0; IQR)	0.0 (0.0, 1.5; IQR)	0.000‡
Contralateral central node metastasis	0.0 (0.0, 1.0; IQR)	0.0 (0.0, 0.0; IQR)	0.047‡

IQR interquartile range

* Student's *t*-test

† Fisher's exact test

‡ Mann–Whitney test

§ Pearson's chi-square test

dissection, and there is no risk of lymphedema [21, 22]. Additionally, other investigators have shown that central compartment dissection can be achieved with low morbidity when performed by an experienced surgeon [23–25]. According to the revised American Thyroid Association 2009 guidelines, routine central compartment neck dissection may be performed in patients with PTC even with clinically uninvolved central neck lymph nodes (recommendation rating: C) [26].

Occult metastasis in the lateral neck compartment

The surgical extent for lateral compartment metastasis in PTC patients remains controversial. At present the surgical management of lateral neck lymph nodes varies from "berry picking" to modified radical neck dissection (MRND) [1, 27, 28]. Despite the controversy surrounding the range of approaches, the revised American Thyroid Association 2009 guidelines suggest that functional compartmental resection may reduce the risk of recurrence, and possibly death, in those patients with clinically evident nodal disease [26, 29–31]. However, in patients without definite lymph node metastasis in the lateral compartment, the routine implementation of MRND is questionable despite a high incidence of metastasis in the lateral compartment (15.9–62.0%) [29, 32–34]. The concern is that MRND is accompanied by a large incision in the neck, longer operative times, and the risk of other complications, like lymphorrhea and nerve and vessel injuries. We hypothesized that if LSLNB selectively detected the patients with occult lateral metastasis that had gone undetected by conventional diagnostic modalities preoperatively, it might decrease future lateral neck recurrences. In the present study, the rate of occult metastasis was 31.7% (19/60) without definite evidence of lateral neck metastasis preoperatively. Therefore, SLNB can be a substitute for routine lateral neck node dissection for the exploration and management of the lateral compartment in patients without definite evidence of lateral neck metastasis.

We are currently conducting a randomized clinical trial in patients with PTC larger than 1 cm and/or with clinically

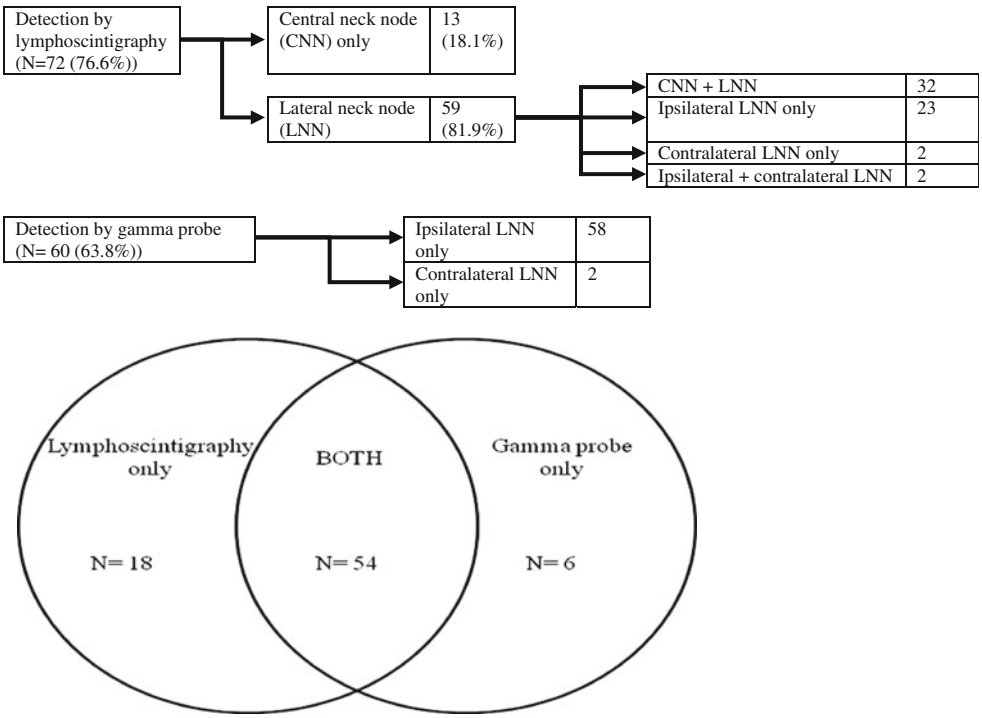

Fig. 1 Lymph nodes detected by lymphoscintigraphy

Table 3 Sentinel lymph node distribution

	Level	No. SLN detected (%)	No. metastatic SLN
SLN level			
Ipsilateral	II	8 (4.6)	4
	III	71 (40.8)	9
	IV	91 (52.3)	16
Contralateral	III	4 (2.3)	0
Total		174 (100)	29

suspicious central neck node metastasis in order to evaluate the efficacy of LSLNB in the prevention of lateral neck recurrence. The patients are randomly assigned to one of two groups, LSLNB or no LSLNB as a control. After completion of the ongoing trial, the impact of occult metastasis and the usefulness of LSLNB will be clear. For the moment, the question remains: Is SLNB the proper method for occult metastasis detection in the lateral compartment?

SLNB for the lateral compartment in PTC patients

Study of the role of LSLNB in PTC patients is rare. One report identifying LSLNB with blue dye showed the usefulness of SLNB for the detection and management of lateral neck node metastasis [18]. In the present study, we perform LSLNB using a radioisotope only. During lateral neck node exploration, searching the lymphatic flow or lymph node for blue dye uptake is not easy due to limitation in the operation field. However, with a radioisotope, searching and localization of the SLN in the lateral neck is easily accomplished with a gamma probe and lymphoscintigraphy, even when the SLN is located in the upper (level I or II) or contralateral neck. The initial detection rate of lateral neck SLN was 63.8% in this study. This was relatively low, but after the early learning curve with this technique the detection rate of SLNB for the lateral compartment increased to 73.1%. In 60 patients with 174 SLNs detected by isotope, the most common location of lateral neck SLNs was level IV (52.3%) (Table 3). We also detected eight SLNs in level II and four SLNs in the contralateral compartment (Table 3). Identification of these nodes might have been difficult with the blue dye only method. This study is the first attempt at detecting lateral neck SLN with a radioisotope.

In order to fully evaluate the accuracy of SLNB for the lateral neck compartment, routine MRND would have been performed inclusively, even in patients with negative SLN. This is the limitation of our study. However, routine performance of lateral neck dissection in the patients with clinically negative lateral neck nodes may constitute an ethical issue. Therefore, our trial was carried out on the basis of the current perception (high rate of metastasis in the lateral compartment) and the hypothesis that LSLNB can selectively detect the patients with occult lateral neck metastasis.

This led us to ask, when do we consider the lateral neck sentinel lymph node biopsy?

Table 4 Analysis of cases with metastatic lateral sentinel lymph node

Case	Sex/ age	Operation name	Tumor size	Tumor location/ injection site	No. of total dissected LN	No. of metastatic LN				Comment
						Central neck	Lateral neck	Metastasis SLN/detected SLN (level)	Non-SLN (level)	
1	F/55	TT + MRND	2.50	Right/ right	46	0	2	1/2 (IV)	1 (IV)	Skip metastasis
2	F/58	TT + MRND	0.80	Right/ right	41	0	3	1/4 (III)	1 (II), 1(III)	Skip metastasis
3	F/62	TT + MRND	0.70	Right/ right	58	4	3	3/15 (IV)	0	SLN only metastasis in lateral neck
4	F/44	TT + MRND	3.10	Both/ left	29	3	4	1/2 (II), 1/1 (III)	2 (IV)	
5	M/35	TT + MRND	1.20	Right/ right	29	1	2	2/3 (IV)	0	SLN only metastasis in lateral neck
6	F/42	TT + MRND	1.20	Both/ right	52	5	1	1/1 (III)	0	SLN only metastasis in lateral neck
7	F/37	TT + MRND	1.30	Left/left	61	5	1	1/1 (III)	0	SLN only metastasis in lateral neck
8	F/66	TT + MRND	1.50	Right/ right	37	8	4	2/2 (IV)	1 (II), 1 (III)	
9	F/32	TT + MRND	1.40	Right/ right	27	8	5	2/2 (II), 1/2 (IV)	2 (III)	
10	M/46	TT + MRND	1.70	Right/ right	27	4	2	1/1 (III)	1 (II)	
11	F/28	TT + MRND	1.30	Left/left	34	6	2	1/1 (IV)	1 (III)	
12	F/25	TT + MRND	1.20	Both/left	69	11	3	0/1 (II), 2/2 (IV)	1 (II)	
13	F/31	TT + MRND	3.00	Left/left	42	6	8	2/2 (III)	3 (III), 3 (IV)	
14	F/27	TT + MRND	1.00	Both/ right	40	7	4	1/4 (III)	2 (III), 1 (IV)	
15	F/45	TT + CND[a]	1.20	Left/left	9	0	1	1/2 (IV)	0	Skip metastasis
16	F/42	TT + CND[a]	1.80	Left/left	22	3	2	2/7 (IV)	0	
17	F/38	TT + CND[a]	1.20	Left/left	8	2	1	1/2 (IV)	0	
18	M/54	TT + CND[a]	1.30	Right/ right	13	2	1	1/5 (III)	0	
19	M/38	TT + CND[a]	1.10	Both/left	14	7	1	1/2 (II)	0	

[a] No metastasis on frozen section, metastasis on permanent pathology report

F female; *M* male; *TT* total thyroidectomy; *CND* central neck node dissection; *MRND* modified radical neck dissection; *SLN* sentinel lymph node

Factors predictive of metastasis in lateral compartment

Many factors for predicting lateral neck node metastasis in PTC patients have been proposed. Chung et al. suggested that younger age, larger tumor size, multiplicity, bilaterality, encapsulation, extrathyroid extension, and lymphatic invasion were associated with LN metastasis in the central or lateral compartments [34]. Qubain et al. showed that tumor size is significantly associated with an increase in metastasis in the lateral compartment and demonstrated the strong relationship between tumor location and lateral neck metastasis in PTC patients [35]. Some authors have insisted that the nodal status of the central compartment is a reliable indicator of lymphatic invasion of the lateral compartment [28, 29, 33]. In the present study, occult metastasis in the lateral compartment was only related with the presence of metastasis in the central neck compartment. Patient age, gender, tumor size, location, extent of tumor invasion, multiplicity, and presence of thyroiditis did not show statistical significance (Table 2). The estimated number of central LN metastases for predicting lateral metastasis using the ROC curve was 2.5. In cases with suspicious multiple central neck node metastases, we recommend lateral neck SLNB for detecting occult metastasis.

Locations and metastatic patterns of SLN and their clinical application

In the present study, 174 SLNs in 60 patients were identified and 170 SLNs in 58 patients were located in the ipsilateral lateral neck compartment, while four SLNs in 2 patients were located in the contralateral level III lateral neck compartment only. Levels IV and III are the most commonly involved locations of SLNs. In level II, eight SLNs in 5 patients (8.3% of total SLN detected patients) were detected, and four SLNs in 3 patients showed metastasis (3/5; 60%).

The reported incidence of metastasis to level II and level IIb in PTC patients is variable (12.7–60% in level II and 2.1–22% in level IIb) [36–39]. Some investigators have insisted that neck dissection should include all node stations, including level IIb [38]. In contrast, others have shown low incidences of metastasis at level II in cases without multilevel neck node metastasis and have suggested that the dissection of level IIb in PTC patients may be required only in those with multilevel neck metastases or with metastases in level IIa [36, 37, 40]. In the present study, level II metastases were detected in 6 of 14 patients (patients 2, 4, 8, 9, 10, and 12 in Table 4) who underwent MRND (42.9%), a relatively high incidence. Among 5 patients with SLNs located in level II, 3 (60%) patients had SLN metastasis. There were no metastases in level V.

Among 14 patients who underwent MRND, 4 showed metastasis in SLN only. In 10 patients who showed both SLN and non-SLN metastasis, we did not find any relationship between the metastases in SLNs and those in non-SLNs (Table 4). Therefore, we suggest that the dissection of all compartments (levels II, III, and IV) except level V should be included for management of PTC patients when metastasis to SLNs in the lateral neck compartment is detected.

In the present series nodal metastasis to a lateral neck node without any central compartment LN metastasis (skip metastasis) was observed in three cases. Several studies had reported skip metastasis in PTC patients [14, 23, 32, 34, 41]. Because of the association between nodal metastasis and local recurrence [42], skip metastasis is likely to accompany a moderate risk of local recurrence. These findings also support the usefulness of SLNB in the lateral neck compartment.

Conclusions

Sentinel lymph node biopsy in the lateral neck compartment could be used preoperatively to detect hidden metastatic lateral neck LNs in patients with papillary thyroid cancer.

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