

Original Article



Is the Internal Jugular Node Dissection without Level V Sufficient in Patients with Papillary Thyroid Carcinoma with Lateral Neck Node Metastasis?

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Conflicts of Interest

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

ABSTRACT

Purpose: Papillary thyroid carcinoma (PTC) has a high rate of lateral neck node metastases, and completeness of surgical resection is an important determinant of outcomes. The appropriate extent of therapeutic lateral neck dissection remains controversial. This study aims to access the impact of lateral neck node dissection of levels II to V in a large patient series.

Methods: A retrospective review of the clinical charts and hospital records of 778 consecutive patients who had metastatic PTC and who underwent unilateral cervical lymph node dissection at a single institution between 1999 January and 2009 December.

Results: A total of 489 modified radical neck dissection (MRND) (levels II–V) and 289 internal jugular node dissection (IJND) (levels II–IV) were performed in 778 patients. There were no differences in clinicopathological findings except for the retrieved and metastatic lateral lymph nodes (LLNs). The multiple-level lymph node (LN) metastasis was more prevalent in the MRND group, and the distribution of metastasis lymph node levels was significantly different in both group. The recurrence rate and disease-free survival were similar in the 2 groups. In multivariate analysis, female sex, tumor size, and multi-level LLN metastasis were independent predictors recurrence. Postoperative complications were similar in MRND and IJND group.

Conclusion: IJND achieves favorable postoperative results in PTC with lateral neck node metastasis patients, and level V metastasis/recurrence incidence is low. Therefore, the extent of lateral neck node dissection, whether IJND or MRND, can be considered for patients according to the simultaneous metastasis level and the tumor size.

Keywords: Thyroid carcinoma; Neck dissection; Recurrence

INTRODUCTION

The incidence of papillary thyroid carcinoma (PTC), the most common malignancy originating from thyroid gland, is increasing worldwide. In Korea, the annual incidence of thyroid cancer rose from 6.3 cases per 100,000 in 1999 to 51.1 cases per 100,000 in 2017, which represents a 22.4% annual increase over the last 10 years (1).

Authors Contributions

Conceptualization: Cho Rok Lee, Kee-Hyun Nam; Data curation: Jin Kyong Kim, Sang-Wook Kang, Jandee Lee, Jong Ju Jeong; Formal analysis: Jin Kyong Kim, Sang-Wook Kang, Jandee Lee, Jong Ju Jeong; Supervision: Woong Youn Chung; Validation: Woong Youn Chung; Writing - original draft: Cho Rok Lee; Writing - review & editing: Kee-Hyun Nam.

PTC has a good prognosis, but it has a high incidence of lymph node (LN) metastasis, occurring in 30%–80% in central neck and in 10%–30% in lateral neck (2-5). In cases of lateral lymph node metastasis (LNM) from PTC, lateral neck node dissection (LND) for clinically evident metastasis is the treatment of choice (6). Since the first description of radical neck dissection (RND) in head and neck cancer patients was published by Crile in 1906 (7), a systemic en bloc resection of the lymphatics of the neck has been an important modality to control of regional metastasis. During the past 100 years, the extent of LND in head and neck cancer has evolved from a single, radical operation to a variety of operations that are selected according to the extent of the metastatic tumor in the neck and to the location of the primary tumor.

Although American Thyroid Association (ATA) guideline recommended that therapeutic lateral neck compartmental LN dissection should be performed for patients with biopsy-proven metastatic lateral cervical lymphadenopathy (8). LND should include level II, III, IV, and V, formal modified radical neck dissection (MRND) has more risk of injury of spinal accessory nerve (SAN) and sensory nerve branches such as greater auricular, cervical cutaneous, and supraclavicular nerves (9,10). Therefore, controversy remains among surgeons about whether it is necessary to dissect level V LNs in all PTC patients with LNM. Currently, most surgeons recommend formal MRND, sparing the SAN, internal jugular vein, and the sternocleidomastoid muscle (11), while some surgeons support internal jugular node dissection (IJND) in low-risk PTC with LNM (level II–IV, but not level V) cautiously to decrease complications after neck dissection (12-14). Until now, few comparative studies have been done on long-term follow-up outcomes after LND with or without level V LN (15-17). Hence, in this study, we evaluated and compared the surgical outcomes of IJND without level V and MRND in patients with PTC with LNM to determine if the extent of lateral LN dissection affected recurrence and survival rates.

MATERIALS AND METHODS

We retrospectively reviewed the medical records of 1,136 consecutive patients with PTC and LNM who underwent bilateral total thyroidectomy with central compartment neck dissection (CCND) and ipsilateral LND from January 1999 to December 2009 in the Department of Surgery, Severance Hospital, Korea. Among these patients, 358 were excluded due to insufficient medical records, short follow-up periods with less than 2 years, non-PTC, non-proven lateral neck node metastasis in the final pathology report, and synchronous distant metastasis at the initial diagnosis. We also excluded PTC with bilateral LN metastasis and patients who underwent LND due to lateral neck node recurrence after initial bilateral total thyroidectomy. Therefore, a total of 778 patients were finally enrolled in the study.

Patients were classified 2 groups as those who had performed formal MRND and IJND, retrospectively. The MRND group comprised 489 patients and IJND group 289 patients. The indications of IJND were small tumor size, single LLN metastasis, not palpable or suspicious metastasis LN in US or CT in level V. We compared the clinicopathological characteristics, surgical outcomes, such as operation time, hospital stays, and number of retrieved LNs, postoperative complications, recurrence rate and pattern, and disease-free survival (DFS) in the 2 groups.

All patients were diagnosed as having PTC by preoperative ultrasonography (US)-guided fine needle aspiration biopsy (FNAB). Staging neck ultrasonography (US) and a neck computed tomography (CT) scan were performed to evaluate preoperative clinical stages (18).

All study subjects had clinically palpable LNNs or a lateral LN suspected of a metastasis by preoperative US staging. The LNM was confirmed by FNAB for the node, and thyroglobulin (Tg) measurement in the wash-out of needles used for FNAB (19) was performed to determine whether the patient needed therapeutic LND. Cervical LN levels were defined using the Memorial Sloan Kettering Cancer Center nomenclature, where level I represented submental and submandibular group; level II, III and IV represented upper, mid, and lower jugular groups, respectively; and level V represented the posterior triangular group (20).

The extent of LN dissection for unilateral MRND routinely performed at our institution includes CCND and LND (II, III, IV, and V), whereas the SND procedure included CCND and LND (II, III, and IV) without the dissection of level V. During surgery, the cervical LN levels present in dissected specimens were classified individually by the supervising surgeon.

After surgery, all patients were treated with levothyroxine to suppress thyroid-stimulating hormone. All patients received high-dose (150 mCi) radioactive iodine (RI) therapy without a diagnostic ^{131}I whole-body scan in order to avoid a “stunning effect” (i.e., decreased uptake by a thyroid remnant of ^{131}I after diagnostic administration of ^{131}I) (21). RI with 100–150 mCi was administered 8–12 weeks after TT (demand for RI in Korea delayed RI therapy in some cases), when each patient was in hypothyroidism after levothyroxine had been withdrawn for 4 weeks and a low-iodine diet had been maintained for 2 weeks. Patients received written instructions and were assisted by a dietician. The ^{131}I whole-body scan was taken on the second day after RI treatment. We regularly followed all patients by neck US and serum Tg at intervals of 3 or 6 months to examine whether there were any findings to indicate local recurrence. Either chest x-ray or CT scan was also performed once per year to detect potential lung metastases. Recurrence-free intervals were defined as the periods from the date of initial surgery to the date at which recurrence was diagnosed by neck US or CT plus cytological examination (when necessary).

This study was approved by the Institutional Review Board of Yonsei University College of Medicine.

Statistical analysis was performed using SPSS statistical software (version 23.0, SPSS, Chicago, IL, USA). Continuous, quantitative data are expressed as the mean±standard deviation, and categorical, qualitative data as frequencies and percentages. The 2 groups were compared using χ^2 test, the Mann-Whitney U test, the Student's t test, or Fisher's exact test for qualitative or quantitative variables, as appropriate. For multivariate analysis for the risk factors for recurrence, multivariate logistic analysis and the Cox-hazard regression model were employed. The Kaplan-Meier method with log rank test was used to calculate survival rates between 2 groups. P values <0.05 were considered statistically significant.

RESULTS

The clinical characteristics of both groups are shown in **Table 1**. The 2 groups were well matched for age and sex ratio (P=NS). There were no significant differences in clinical findings between the 2 groups, except for number of retrieved and pathologically proven metastatic lateral LNs. The numbers of retrieved lateral LNs (30.5 ± 11.9 vs. 25.4 ± 9.6 , $P=0.045$) and pathologically proven metastatic lateral LNs (5.4 ± 4.5 vs. 4.8 ± 3.6 , $P=0.001$) were significantly greater in the MRND group. In addition, there no significant differences in

Table 1. Clinicopathologic characteristics of the 2 groups

Variables	Total (n=778)	MRND (n=489)	IJND (n=289)	P value
Age (yr)				0.141
<55	589 (75.7)	379 (77.5)	210 (72.7)	
≥55	189 (24.3)	110 (22.5)	79 (27.3)	0.426
Sex				
Female	615 (79.1)	385 (78.7)	230 (79.6)	
Male	163 (21.0)	104 (21.3)	59 (20.4)	
Retrieved central LNs(N)	7.6±5.6	7.7±5.7	7.5±5.6	0.247
Metastatic central LNs (N)	3.9±3.6	4.0±3.7	3.7±3.6	0.641
Retrieved lateral LNs (N)	28.6±11.4	30.5±11.9	25.4±9.6	0.045
Metastatic lateral LNs (N)	5.2±4.2	5.4±4.5	4.8±3.6	0.001
Tumor size (cm)				0.896
≤1	255 (32.8)	160 (32.7)	95 (32.9)	
>1 and ≤2	329 (42.3)	205 (41.9)	124 (42.9)	
>2 and ≤4	173 (22.2)	112 (22.9)	61 (21.1)	
>4	21 (2.7)	12 (2.5)	9 (3.1)	
Multiplicity				0.711
No	416 (53.5)	264 (54.0)	152 (52.6)	
Yes	362 (46.5)	225 (46.0)	137 (47.4)	
Bilaterality				0.157
No	518 (66.6)	335 (68.5)	183 (63.3)	
Yes	260 (33.4)	154 (31.5)	106 (36.7)	
Capsule invasion				0.045
No	145 (18.6)	102 (20.9)	43 (14.9)	
Yes	633 (81.4)	387 (79.1)	246 (85.1)	
Central LN metastasis				0.567
No	143 (18.4)	93 (19.0)	50 (17.3)	
Yes	635 (81.6)	396 (81.0)	239 (82.7)	
Distant metastases	27 (3.5)	14 (2.9)	13 (4.5)	0.480
Distribution of pathologic LLNs				
Level 2	394 (50.1)	262 (53.5)	132 (45.7)	
Level 3	589 (75.1)	361 (73.8)	228 (78.9)	
Level 4	521 (66.3)	314 (64.2)	207 (71.6)	
Level 5	96 (12.3)	96 (19.6)	0	
Multiple-level LLN metastasis				0.004
No	223 (28.7)	133 (27.3)	90 (31.1)	
Yes	555 (71.3)	356 (72.7)	199 (68.9)	
Metastatic lymph node levels				0.006
1 level	223 (28.7)	133 (27.3)	90 (31.1)	
2 levels	301 (38.7)	181 (37.1)	120 (41.5)	
3 levels	226 (29.1)	148 (30.3)	78 (27.0)	
4 levels	26 (3.3)	25 (5.1)	1 (0.3)	
5 levels	1 (0.1)	1 (0.2)	0	

MRND = modified radical neck dissection; IJND = internal jugular node dissection; LN = lymph node; LLN = lateral lymph node.

terms of tumor size, multiplicity, bilaterality, capsule invasion, and the central LN metastasis. Incidence of multiple-level LN metastases was higher in MRND group, and the distribution of metastasis LN levels was significantly different in both group.

The median follow up period were 94.3±37.6 months. During follow-up, local or distant recurrence developed in 84 patients, consisting of 57 (11.7%) in MRND and 27 (9.3%) in IJND group. The 10-year DFS was 88.3% for MRND and 90.3% for IJND group, and 15-year DFS was 88.0% in MRND and 89.5% in IJND group. The mean recurrence-free interval was 44.1±33.6 months for MRND and 47.3±37.1 months for IJND group ($P=0.694$). No significant differences between the 2 groups were found regarding DFS ($P=0.283$) and recurrence rate ($P=0.188$) (Table 2).

Table 2. The treatment outcomes of the 2 groups

Variables	Total (n=778)	MRND (n=489)	IJND (n=289)	P value
5-year disease free survival	95.9%	93.6%	90.9%	0.283
10-year disease free survival	91.8%	88.3%	90.3%	0.283
15-year disease free survival	89.2%	88.0%	89.5%	0.283
Recurrence rate	10.8% (84/778)	11.7% (57/489)	9.3% (27/289)	0.188
Recurrence-free intervals	45.2±34.6	44.1±33.6	47.3±37.1	0.694

MRND = modified radical neck dissection; IJND = internal jugular node dissection.

Table 3. Cox regression analysis of the relationship between clinicopathologic factors and recurrence

Variables	Univariate analysis		Multivariate analysis	
	OR (95% CI)	P value	OR (95% CI)	P value
Age (yr): ≥55 vs. <55	1.513 (0.957–2.391)	0.076		
Sex: male vs. female	2.059 (1.313–3.229)	0.002	1.619 (1.015–2.583)	0.043
Operation method: MRND vs. IJND	0.779 (0.493–1.231)	0.284		
Tumor size (continuous variable)	1.638 (1.433–1.873)	0.001	1.533 (1.329–1.769)	0.001
Multiplicity	1.312 (0.855–2.014)	0.213		
Bilaterality	1.502 (0.973–2.318)	0.066		
Capsule invasion	0.201 (1.012–4.034)	0.046	0.596 (0.297–1.196)	0.145
Central LN metastasis	0.998 (0.580–1.723)	0.920		
Multiple-level LLN metastasis	1.904 (1.131–3.207)	0.015	1.596 (1.044–2.699)	0.041

OR = odds ratio; CI = confidence interval; LN = lymph node; LLN = lateral lymph node; MRND = modified radical neck dissection; IJND = internal jugular node dissection.

The risk factors for recurrence were evaluated using univariate and multivariate logistic regression analyses for all study populations. The univariate analysis showed that female gender, tumor size, capsule invasion, and multiple-level LLN metastasis were risk factors for recurrence, whereas age group divided by 55 years of age, operation method (MRND vs. IJND), multiplicity, bilaterality, and central LN metastasis were not significantly associated with recurrence. However, when these variables were included in multivariate logistic regression models, female gender, tumor size, and multiple-level LLN metastasis were risk factors for recurrence. The extent of LND, the main concern of this study, was not significantly associated with recurrence (**Table 3**).

In analysis of recurrence patterns, 7 patients in the MRND group had distant recurrence in lung and 55 patients had local recurrences that were mostly observed in level IV, followed by level III. In the IJND group, 7 patients had distant recurrence in lung and 1 patient died of simultaneous lung and bone recurrence. Twenty-four patients had local recurrences, the most common site being level IV, followed level III. There were 4 patients in MRND and 1 patient in IJND diagnosed with recurrence in level V (**Table 4**).

Perioperative complications were compared between groups (**Table 5**). No significant differences in the frequency of complications were found. The incidence of permanent SAN injury was 0.8% in the MRND group and 0% in the IJND group.

DISCUSSION

Although lymphatic metastasis does not affect overall survival in PTC patients, there is a general consensus that cervical LN metastasis is the most significant prognostic factor for locoregional recurrences (22–24). This uncertainty of the prognostic impact of LN metastasis on overall survival and risk of postoperative morbidity after formal MRND contributes to the continuing debate about whether it is mandatory to dissect level V LNs in all PTC patients with lateral LN metastases.

Table 4. Distribution of recurrence in the 84 patients in 2 groups

Variables	Total (n=84)		MRND (n=57)		IJND (n=27)	
Local recurrence (single or multiple)	79 (10.8%)		55 (11.7%)		24 (9.3%)	
Total	79 (10.8%)		55 (11.7%)		24 (9.3%)	
Recur side	Ipsilateral 46	Contralateral 33	Ipsilateral 34	Contralateral 21	Ipsilateral 11	Contralateral 13
Level I	1		1			
Level II	12	11	8	7	4	4
Level III	8	20	7	12	1	8
Level IV	13	23	8	16	5	7
Level V	3	2	2	2	1	0
Level VI	21	13	18	9	3	4
Level VII	4	1	4	0	0	1
Distant recurrence						
Lung	14		7		7	
Lung and bone	1		0		1	

MRND = modified radical neck dissection; IJND = internal jugular node dissection.

Table 5. Comparison of perioperative complications in 2 groups

Complications	Total	MRND	IJND	P value
Transient hypocalcemia	285 (36.6)	185 (37.8)	100 (34.6)	0.397
Permanent hypocalcemia	43 (5.5)	29 (5.9)	14 (4.8)	0.627
Transient hoarseness	14 (1.8)	10 (2.0)	4 (1.4)	0.588
Permanent RLN injury	11 (1.4)	9 (1.8)	2 (0.3)	0.227
Chyle leakage	43 (5.5)	31 (6.3)	12 (4.2)	0.255
Hematoma	8 (1.0)	4 (0.8)	4 (1.4)	0.478
Seroma	72 (9.3)	49 (10.0)	23 (8.0)	0.372
Permanent SAN injury	4 (0.5)	4 (0.8)	0	0.485
Hornor syndrome	4 (0.5)	3 (0.6)	1 (0.3)	0.525
Infection	3 (0.4)	3 (0.6)	0	0.299

MRND = modified radical neck dissection; IJND = internal jugular node dissection; RLN = recurrent laryngeal nerve; SAN = spinal accessory nerve.

Dissection of level V is associated with postoperative morbidities, such as SAN dysfunction, that decrease patient's quality of life (QOL) postoperatively. The SAN must be identified and retracted to clear away LNs during the dissection of level V. Patten et al. (25) reported that most patients who underwent RND for head and neck cancer experienced pain, weakness, shoulder droop, and movement disability because the SAN had been sacrificed. Kupferman et al. (10) reported that even though the SAN preserved, postoperative shoulder dysfunction occurred in 27% of patients who underwent RND as a result of excessive retraction or ischemia. Also not to be underestimated is the impact on QOL that transection of the cervical rootlets incurs, often resulting in neck numbness or neuropathic pain (26). In our study, permanent SAN injuries were very rare events, with rates of 0% in group I and 1.2% in group II. This finding could be explained by all LND procedures having been performed by an experienced surgeon with a good anatomical knowledge of the SAN course.

Decision on the extent of LND, which is necessary for the treatment of regional metastases from PTC, should be based on predictable drainage patterns. The anterolateral group of nodes (level II, III and IV) is at the greatest risk of LNM, with level III nodes being the most frequently involved (27,28). In our previous study, we found that level IIb and V LNs were rarely metastasized and, therefore, did not necessarily require aggressive dissection. Preoperative nodal evaluation for LNM in PTC patients is essential in determining the inclusion of level V in a LND. Although the LNM could be detected by palpation (5), high resolution US has been widely used for preoperative nodal staging (29,30). Thereafter, the LNM was confirmed by FNAB for the node. In addition, the cystic LNM from PTC can be diagnosed by Tg measurement in the wash-out of needles used for FNAB (19). In our study, all patients who underwent LND underwent preoperative US staging to determine if clinically negative LN in level V.

Consequently, we found that the frequency of LNM for level II and V and the presence of multi-level LNM were significantly higher in the MRND group than the IJND group, suggesting our strategy of the LND based on preoperative nodal evaluation using US could be justified.

Currently, for PTC patients with LLN metastasis, most surgeons prefer formal MRND (level II–V) to gain local control because some studies have demonstrated that high metastatic rates in level V nodes from 25% to 60% (11,13,27). On the other hand, in several recent studies, authors have recommended a selective approach to LND in PTC patients with LNM. Turanli (12) reported in a comparative study of 61 patients who underwent SND or MRND that the type of dissection was not related to DFS, overall survival, and local recurrence. Kandil et al. (31) reported that extensive neck dissection such as MRND among PTC patients did not result in an improved survival benefit compared with no LN dissection or SND. Caron et al. (13) reported that recurrence at levels I and V were uncommon in 106 PTC patients with LNM. They concluded that levels I and V did not require resection unless there is clinical or radiological evidence of disease. Our data regarding treatment outcomes correspond with these previous studies (12,31), suggesting that there was no difference between IJND and MRND groups regarding DFS and recurrence rate. Furthermore, multivariate analysis of this study revealed that the type of LND was not significantly associated with recurrence, and female gender, tumor size, and multiple-level LLN metastasis were independent risk factors for recurrence. Our findings indicate that the local recurrence after complete nodal dissection regardless of the type of LND is still related to aggressive factors like tumor size and LLN metastasis levels, which are known to be important prognostic factors in PTC.

The local recurrence rate after LND was reported to be 8%–32% (12,22). The present study showed of recurrence rate of 10.8% (11.7% in the MRND group and 9.3% in the IJND group) in all the groups compared with previous studies. This reason is that the IJND (level II–IV) performed in this study apply the same comprehensive anatomic dissection as the MRND and harvesting metastases cleared all lymphatic tissue at each level. Therefore, our results showed a significant reduction in the rate of recurrence. At our institute, a berry-picking procedure is not accepted for the surgical treatment of PTC nodal metastases, because it was reported to increase death rates due to recurrence in PTC patients (32).

In assessing recurrence at level V in patients who underwent IJND without level V, our results, which are in accordance with those of the study by Caron and Clark (6) that showed 5 recurrence of total at level V, revealed that only 1 recurrence in level V occurred in the IJND group. The present study may be confronted with debate over the possibility of existence of occult level-V metastases in the IJND group, because Roh et al. (33) reported metastases detected only on postoperative pathological examination (pN1b) were present in a number of level-V specimens (16%–20%). Furthermore, recent studies to identify predictors of level V LLN metastasis demonstrated that simultaneous metastases to level II, III and IV, tumor multifocality, perineural invasion, and macroscopic extranodal extension were significant predictors in PTC patients with nodal metastases (11,34,35). However, these studies could be criticized because of the lack of long-term outcomes according to the type of LND. On the other hand, there are data suggesting that occult LLN metastasis or recurrence does not affect overall survival in PTC patients. Ito et al. (36) reported that pN1b did not independently affect the cause specific survival of patients. Noguchi and Murakami (37) reported that at least 75% of patients with PTC have occult LN metastases, but only about 20% become clinically evident, which means pN1b rarely developed sufficiently to be evident. In addition to these studies, our data support that patients with a clinically

negative level-V LN, although they might have occult LN metastases, would be expected to have lower recurrence rate.

This study has several limitations. First, the patient group divided not from the randomized control design but the operation method already performed and the study could have some inevitable features. Even though the clinicopathologic characteristics were not markedly different between the 2 groups, the IJND was performed on selected patients. Second, due to the long-term period of data enrollment, different radiologists and surgeons were involved in the evaluation and management of patients, resulting in possible inter-observer variability in the interpretation of metastasis.

Despite these limitations, our study had several strong points. First, this study has a relatively long-term follow-up period. Second, 778 cases of N1b patients were analyzed, which makes it a large study regarding the extent of lateral neck dissection.

In conclusion, IJND achieves favorable postoperative results in PTC with lateral neck node metastasis patients, and level V metastasis and recurrence incidence was low. Therefore, the extent of lateral neck node dissection, whether IJND or MRND, can be considered for patients according to the simultaneous metastasis level and the tumor size.

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