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ORIGINAL ARTICLE

Optimal extent of prophylactic central neck dissection for papillary thyroid carcinoma: Comparison of unilateral versus bilateral central neck dissection

Han Seok Yoo, Myung Chul Shin, Yong Bae Ji, Chang Myeon Song, Seung Hwan Lee, Kyung Tae*

Department of Otolaryngology—Head and Neck Surgery, School of Medicine, Hanyang University, Seoul, Republic of Korea

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Summary *Objective:* The aim of the study was to determine the optimal extent of prophylactic central neck dissection (pCND) in papillary thyroid carcinoma (PTC).
Materials and methods: We studied 384 patients with clinically node-negative unilateral PTC who had undergone total thyroidectomy with pCND. Of these, 169 patients underwent unilateral pCND, and 215, bilateral pCND.
Results: Age, sex, and TNM stage did not differ between the two groups. The rates of occult central lymph node metastasis were 34.3% and 37.2% in the unilateral and bilateral pCND groups, respectively ($p = 0.558$). Metastasis to the contralateral paratracheal lymph node occurred in 4.2% of the bilateral pCND group. Major complication rates did not differ between the two groups, except for transient hypoparathyroidism, which was higher in the bilateral group (43.7% vs. 33.7%, $p = 0.047$). Stimulated thyroglobulin and RAI ablation uptake rates were similar in the two groups, as were recurrence and disease-free survival.
Conclusion: Contralateral paratracheal node dissection may be not indicated for prophylactic central neck dissection in clinically node-negative unilateral PTC because the rate of contralateral paratracheal node metastasis is low and transient hypoparathyroidism is higher following bilateral dissection.

* Corresponding author. Department of Otolaryngology—Head and Neck Surgery, School of Medicine, Hanyang University, 222 Wangshimni-ro, Seongdong-gu, Seoul 04763, Republic of Korea.
E-mail address: kytae@hanyang.ac.kr (K. Tae).

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1. Introduction

Papillary thyroid carcinoma (PTC) accounts for > 80% of all thyroid malignancies.[1] It is generally slow-growing and the overall prognosis is excellent, with 5-year, 10-year, and 20-year survival rates of 94%, 89%, and 87%, respectively.[1,2] Cervical lymph node metastasis occurs frequently in PTC and is an unfavorable prognostic factor, especially in patients over 45 years.[3–5]

The central neck compartment is considered to be the primary echelon of lymph node metastasis in PTC. The occult metastasis rate ranges from 20% to 90% in patients who have undergone prophylactic central neck dissection (pCND).[6–8]

Although PTC has an excellent prognosis, locoregional recurrence has been reported in up to 30% of patients. It is related to increased morbidity and mortality rates, and a poor prognosis.[9–11] Locoregional recurrence was more frequent in patients with lymph node metastasis than in those without it.[12] Also, extracapsular spread of metastatic lymph nodes and maximal extrathyroidal extension of tumors are important prognostic factors for locoregional recurrence in PTC.[13,14]

Therapeutic central neck dissection should be carried out in patients with clinically node-positive PTC.[8] However, pCND remains controversial in patients with node-negative PTC because of a lack of substantial evidence of the benefit, and the potential morbidity of the procedure.[15,16] Some expert thyroid surgeons prefer to perform pCND because occult micrometastasis is common and pCND can be performed safely without extending the incision during the initial thyroidectomy and may decrease lymph node recurrence.[17–19] Also pCND provides more accurate staging for decisions regarding adjuvant RAI ablation.

Besides the controversy regarding pCND itself, the optimal extent of pCND is also controversial. There is no consensus on the extent of pCND (unilateral vs. bilateral). The aim of this study was to determine the optimal extent of pCND in patients with PTC by comparing unilateral pCND with bilateral pCND in terms of surgical outcomes, complications, recurrence, and survival.

2. Materials and methods

Between January 2001 and December 2011 in our institute, 953 patients underwent thyroidectomy for PTC. Of them, 814 (85%) underwent total thyroidectomy and 139 (15%) underwent thyroid lobectomy. In terms of CND, 729 (76.5%) underwent CND with thyroidectomy (therapeutic CND in 91 cases and prophylactic CND in 638 cases), and 224 (23.5%) did not undergo CND. We excluded patients who did not undergo pCND with thyroidectomy. We also excluded cases with other pathologic types of thyroid cancer, bilateral PTC, recurrent cases, or distant metastasis, and patients who underwent thyroid lobectomy, concurrent lateral neck dissection, or therapeutic CND. Finally, 384 patients with clinically node-negative unilateral PTC who had undergone total thyroidectomy with pCND were included in this study. The Institutional Review Board of Hanyang University Hospital approved this study.

Preoperative physical examination, ultrasonography (US) and computed tomography (CT) were performed in all patients, and there was no evidence of metastatic cervical lymph nodes on preoperative physical examination, US, and CT. All patients were diagnosed with PTC by preoperative ultrasonography-guided fine needle aspiration cytology (FNAC).

The extent of pCND was decided by surgeon's preference in our institute. Of 384 patients studied, 169 underwent total thyroidectomy with unilateral pCND, and the other 215 underwent total thyroidectomy with bilateral pCND. In bilateral pCND, pretracheal, prelaryngeal, and bilateral paratracheal lymph nodes were removed, and in unilateral pCND, pretracheal, prelaryngeal, and ipsilateral paratracheal lymph nodes were removed.

We compared age, tumor size, multifocality, extrathyroidal extension (ETE), lymphovascular invasion, occult lymph node metastasis rate, complications, recurrence, and survival rate between the two groups. ETE was classified into minimal and maximal ETE. We defined minimal ETE as extension of the primary tumor to the strap muscles or perithyroidal soft tissue, and maximal ETE as extension to surrounding structures such as trachea, esophagus, recurrent laryngeal nerve (RLN), or larynx. Radioactive iodine (RAI) ablation was performed in most cases of maximal ETE or tumors > 4cm, and also in selected patients with minimal ETE or cervical lymph node metastasis, and tumor size 1–4 cm and/or higher risk histologic features similar to the American Thyroid Association (ATA) guidelines.[8] The RAI ablation dose ranged from 30 mCi to 150 mCi. Hypoparathyroidism was defined as any decrease of intact parathyroid hormone below the normal range regardless of hypocalcemic symptoms including tingling sensation, tetany, Chvostek's sign, and Trousseau's sign. It was considered permanent hypoparathyroidism if the decrease of intact parathyroid hormone persisted for > 6 months. Flexible fiberoptic laryngoscopy was performed routinely in all patients on the day before surgery and at 1 day after the operation. It was repeated serially if necessary. Recurrent laryngeal nerve palsy was considered permanent if it lasted > 6 months. Intraoperative neuro-monitoring was not used in this study. Recurrence was defined as a new structural abnormality on imaging studies such as neck US, CT, or whole-body iodine scan. Neck US, whole body iodine scan, and stimulated or suppressed thyroglobulin (Tg) measurements were performed at 6–12 month intervals to detect recurrence after surgery.

Statistical analysis was performed using SPSS version 22.0 (SPSS Chicago, IL, USA). Fisher's exact test and the Chi-square test were used to compare categorical variables between the two groups. Continuous variables were compared by Student t test. Disease-free survival was calculated by the Kaplan–Meier method. A p value < 0.05 was considered statistically significant.

3. Results

The characteristics of the patients in the two groups, and of their tumors, are listed in Table 1. There was no difference in age, sex, duration of follow-up, tumor size, multifocality, ETE, lymphovascular invasion, perineural invasion, T and N classification, and stage between the two groups.

Table 1 Comparison of the clinicopathological characteristics of the unilateral and bilateral central neck dissection groups.

Characteristic	Total thyroidectomy with ipsilateral pCND ($n = 169$)	Total thyroidectomy with bilateral pCND ($n = 215$)	p
Age (y)	48.25 ± 11.76	50.09 ± 12.56	0.14
Sex			0.45
Male	25 (14.8%)	38 (17.7%)	
Female	144 (85.2%)	177 (82.3%)	
Mean follow-up (mo)	58.91 (± 28.55)	60.41 (± 28.67)	0.61
Size of tumor (mm)	10.38 (± 7.29)	11.15 (± 6.48)	0.27
Multifocality of tumor	22/169 (13.0%)	28/215 (13.0%)	0.99
Extrathyroidal extension			0.52
None	90/169 (53.5%)	102/215 (47.4%)	
Minimal	76/169 (45.0%)	108/215 (50.2%)	
Maximal	3/169 (1.8%)	5/215 (2.3%)	
Lymphovascular invasion	21/169 (12.4%)	42/215 (19.5%)	0.062
Perineural invasion	3/169 (1.8%)	6/215 (2.8%)	0.74
T classification			0.68
T1	87(51.5%)	99(46.0%)	
T2	6(3.6%)	6(2.8%)	
T3	74(43.8%)	107(49.8%)	
T4a	2(1.2%)	3(1.4%)	
N classification			0.56
N0	111 (65.7%)	135 (62.8%)	
N1a	58 (34.3%)	80 (37.2%)	
TNM stage			0.394
I	105 (62.1%)	118 (54.9%)	
II	2 (1.2%)	1 (0.5%)	
III	61 (36.1%)	94 (43.7%)	
IVa	1 (0.6%)	2 (0.9%)	

pCND = prophylactic central neck dissection; TNM.

The mean numbers of lymph nodes removed and of metastatic lymph nodes were higher in the bilateral pCND group than the unilateral pCND group (9.25 vs. 5.34, $p < 0.001$ and 1.48 vs. 0.87, $p = 0.015$, respectively). Occult central lymph node metastasis occurred in 58 patients (34.3%) in the unilateral pCND group and 80 (37.2%) in the bilateral pCND group. Among the latter 80 patients, ipsilateral, bilateral, and only contralateral paratracheal lymph node metastasis occurred in 71 (33.0%), five (2.3%), and four patients (1.9%), respectively. Operative time also did not differ between the two groups ($p = 0.59$) (Table 2).

The factors related to contralateral paratracheal node metastasis are listed in Table 3. In univariate analysis, tumor size (> 4cm), age (< 45), and ipsilateral central lymph node metastasis were significantly correlated with contralateral paratracheal lymph node metastasis ($p = 0.044$, $p = 0.049$, and $p = 0.009$, respectively). However, in multivariate analysis only ipsilateral central lymph node metastasis was significantly correlated with contralateral paratracheal node metastasis ($p = 0.042$).

The outcomes of RAI ablation are listed in Table 4. Postoperative RAI ablation was performed in 139 patients (82.2%) in the unilateral pCND group, and 191 patients (88.8%) in the bilateral group. RAI uptake rates at first RAI ablation were 96.4% and 96.9% in the unilateral and bilateral pCND groups, respectively ($p = 0.820$). Stimulated Tg

Table 2 Surgical outcomes in the unilateral and bilateral central neck dissection groups.

Surgical outcome	Total thyroidectomy with ipsilateral pCND ($n = 169$)	Total thyroidectomy with bilateral pCND ($n = 215$)	p
Operative time (min)	154.35 ± 44.40	150.66 ± 51.24	0.59
Resected LN (no.)	5.34 ± 4.04	9.25 ± 9.41	<0.001
Metastatic LN (no.)	0.87 ± 2.13	1.48 ± 5.12	0.015
Central LN metastasis			0.558
Ipsilateral	58/169 (34.3%)	71/215 (33.0%)	0.789
Bilateral	—	5/215 (2.3%)	—
Only contralateral	—	4/215 (1.9%)	—

LN = lymph node; pCND = prophylactic central neck dissection.

Table 3 Logistic regression analysis for contralateral central lymph node metastasis.

Variable		No. of central LNM	Univariate	Multivariate
Size (cm)	≤4	1/108 (0.9%)	0.044	0.169
	>4	8/107 (7.5%)		
Age (≥45 y)	<45	5/55 (9.1%)	0.049	0.132
	≥45	4/160 (2.5%)		
Sex	Female	7/177 (4.0%)	0.716	
	Male	2/38 (5.3%)		
Multifocality	Yes	1/28 (3.6%)	0.862	
	No	8/187 (4.3%)		
ETE	Yes	6/113 (5.3%)	0.393	
	No	3/102 (2.9%)		
Lymphovascular invasion	Yes	3/42 (7.1%)	0.296	
	No	6/173 (3.5%)		
Perineural invasion	Yes	0/6 (0.0%)	0.999	
	No	9/209 (4.3%)		
T classification	T1/T2	3/119 (2.9%)	0.350	
	T3/T4	6/96 (5.5%)		
Ipsilateral central LNM	Yes	8/76 (9.2%)	0.009	0.042
	No	1/139 (1.3%)		

ETE = extrathyroidal extension; LNM = lymph node metastasis.

at first RAI ablation did not differ between the two groups ($p = 0.103$), and stimulated Tg and iodine-131 (^{131}I) whole body scan (WBS) uptake rate in diagnostic ^{131}I WBS after RAI ablation also did not differ ($p = 0.180$ and $p = 0.235$, respectively).

Postoperative complications are listed in Table 5. The rates of transient RLN palsy were 4.7% and 5.6% in the unilateral and bilateral pCND groups, respectively ($p = 0.71$). The rates of permanent RLN palsy were 0.6% in the unilateral pCND group and 0.5% in the bilateral pCND group ($p = 1.00$). Transient hypoparathyroidism rates were significantly higher in the bilateral group than the unilateral group (43.7% vs. 33.7%, $p = 0.047$). However, permanent hypoparathyroidism rates did not differ between the two groups ($p = 0.47$), and the same was true for the rates of hematoma and seroma.

Recurrence occurred in three patients (1.8%) in the unilateral group and seven (3.2%) in the bilateral group ($p = 0.366$) at a mean postoperative time of 60.41 ± 28.67 months (Table 6). In the unilateral group, the sites of recurrence were the ipsilateral central compartment in two patients and the lateral compartment lymph node in one patient. In the bilateral group, two recurrences occurred in the central compartment, three were in the lateral compartment, one in both central and lateral compartment, and one in the lung. Of the 10 patients with recurrence, four patients who showed recurrence in the ipsilateral lateral compartment lymph node underwent selective neck dissection of Levels II–V. Two patients with recurrence in the central compartment underwent revision CND, and one patient with recurrence in both central and lateral neck compartment underwent selective neck dissection and CND together. One patient who showed recurrence in the lung received high dose radioactive iodine therapy. Of the remaining two patients with recurrence in the central compartment, one wanted close follow-up of recurrence without reoperation, and the other one was not followed up. Of eight patients who received treatment for recurrence, seven patients who underwent reoperation are still alive with no evidence of

Table 4 Parameters of radioactive iodine ablation (RAI) in the unilateral and bilateral central neck dissection groups.

Factor	Total thyroidectomy with ipsilateral pCND ($n = 169$)	Total thyroidectomy with bilateral pCND ($n = 215$)	p
No. of patients received first RAI ablation	139/169 (82.2%)	191/215 (88.8%)	0.065
First RAI ablation dose (mCi)	103.58 (±75.49)	101.79 (±68.25)	0.411
Stimulated Tg at first RAI ablation (ng/mL)	6.38 (±10.29)	4.65 (±9.62)	0.103
RAI uptake rate at first RAI ablation	134/139 (96.4%)	185/191 (96.9%)	0.820
No. of patients received WBS after RAI ablation	94/139 (67.6%)	112/191 (58.6%)	0.491
Stimulated Tg at diagnostic WBS after RAI ablation (ng/mL)	1.55 (±4.74)	0.81 (±3.38)	0.180
RAI uptake rate at diagnostic WBS after RAI ablation	4/94 (4.3%)	3/112 (2.7%)	0.235

pCND = prophylactic central neck dissection; RAI = radioactive iodine; Tg = thyroglobulin; WBS = ^{131}I whole body scan.

Table 5 Comparison of complications in the unilateral and bilateral central neck dissection groups.

Complication	Total thyroidectomy with unilateral pCND ($n = 169$)	Total thyroidectomy with bilateral pCND ($n = 215$)	p
Transient RLN palsy	8 (4.7%)	12 (5.6%)	0.71
Permanent RLN palsy	1 (0.6%)	1 (0.5%)	1.00
Transient hypoparathyroidism	57 (33.7%)	94 (43.7%)	0.047
Permanent hypoparathyroidism	2 (1.2%)	6 (2.8%)	0.47
Hematoma	1 (0.6%)	5 (2.3%)	0.235
Seroma	27 (16.0%)	36 (16.7%)	0.84

pCND = prophylactic central neck dissection; RLN = recurrent laryngeal nerve.

Table 6 Comparison of recurrence in the unilateral and bilateral central neck dissection groups.

	Total thyroidectomy with unilateral pCND ($n = 169$)	Total thyroidectomy with bilateral pCND ($n = 215$)	p
Recurrence	3 (1.8%)	7 (3.2%)	0.366
Site of recurrence			
Ipsilateral central compartment	2	1	
Contralateral central compartment		1	
Ipsilateral lateral compartment	1	3	
Ipsilateral central & lateral neck		1	
Distant metastasis		1	
Time to recurrence (mo)	29.33 ± 23.18	48.71 ± 17.46	0.183

pCND = prophylactic central neck dissection.

disease, and one patient with lung recurrence died with disease.

Disease-free survival curves did not differ between the two groups ($p = 0.371$) (Figure 1).

4. Discussion

The optimal extent of prophylactic central neck dissection has not been established. Some studies have suggested that ipsilateral pCND might be adequate for clinically node-negative PTC, because its complication rate is lower than that of bilateral pCND, while providing similar oncologic outcomes.[20] However, other studies have recommended routine bilateral pCND for staging of PTC, which, it is claimed, could improve disease-free survival and locoregional control without increasing permanent complications.[21]

In the present study, we aimed to determine the optimal extent of pCND in patients with PTC. We did not aim to evaluate the rationale for pCND itself. We compared unilateral versus bilateral pCND groups to determine the optimal extent of pCND in clinically node-negative unilateral PTC. The complication rate did not differ between the

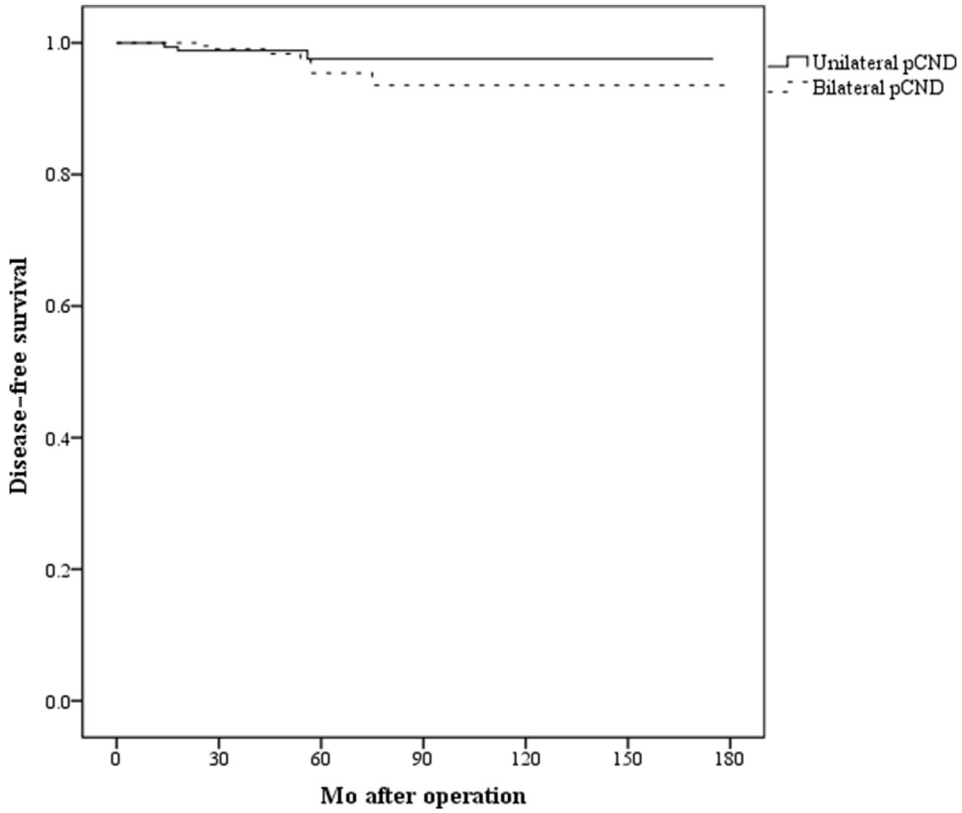

Figure 1 Disease-free survival in patients with clinically node-negative unilateral papillary thyroid carcinoma. The disease-free survival curves of the unilateral and bilateral prophylactic central neck dissection (pCND) groups do not differ significantly. pCND = prophylactic central neck dissection.

two groups, except that transient hypoparathyroidism occurred more frequently in the patients who underwent bilateral pCND (43.7% vs. 33.7%) ($p = 0.047$). This is in accord with other studies in which the rate of transient hypoparathyroidism was lower in the unilateral pCND group than the bilateral group (18–26.8% vs. 35–48.3%).[22–24] The rate of transient RLN palsy was similar in the two groups, again in agreement with previous reports.[22–30]

Postoperative serum Tg level can be used as a surrogate marker for predicting recurrence or persistent disease after total thyroidectomy and RAI ablation.[8,31] In one study there was no significant difference in postablative Tg level between unilateral and bilateral pCND.[22] In our case, stimulated Tg at RAI ablation and during the diagnostic ^{131}I WBS after RAI ablation did not differ between the unilateral and bilateral pCND groups. These results might suggest that unilateral pCND is comparable to bilateral pCND for lowering stimulating Tg in patients with clinically node-negative unilateral PTC.

The incidence of lymph node metastasis to the subsite of the central compartment can be used to decide the extent of central neck dissection. In the present study, the rate of occult contralateral paratracheal node metastasis was just 4.2% in the bilateral pCND group, in agreement with our previous study.[32] Therefore, unilateral CND might be appropriate for prophylactic CND for clinically node-negative unilateral PTC, given the low rate of contralateral paratracheal node metastasis.

In this study, recurrence rate was not significantly different between the unilateral (1.8%) and bilateral (3.2%) pCND groups. Also, disease-free survival did not differ between the two groups. Therefore, unilateral pCND may be comparable to bilateral pCND from the viewpoint of recurrence and disease-free survival, although the follow-up period in the present study was rather short.

In terms of optimal extent of pCND, our results suggest that unilateral pCND may be an appropriate procedure for clinically node-negative unilateral PTC because the rate of contralateral paratracheal node metastasis was relatively low, and it produced comparable serum Tg levels, recurrence rates, and disease-free survival to bilateral CND, although causal less postoperative transient hypoparathyroidism than bilateral CND.

There were some limitations to this study. It was a nonrandomized retrospective study that might have had a patient selection bias, although the clinicopathologic characteristics of the unilateral and bilateral CND groups did not differ. Further studies with prospective randomized controlled trial are needed to overcome the limitations of this study and confirm its findings.

In conclusion, ipsilateral central neck dissection may be a reasonable surgical option for prophylactic CND in unilateral PTC with clinically negative lymph nodes because of its lower rates of contralateral paratracheal node metastasis and transient hypoparathyroidism than bilateral pCND.

Conflicts of interest

The authors have no conflicts of interest.

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