Comparison of Long-Term Outcomes Between Ipsilateral and Bilateral Central Neck Dissection in Occult Contralateral Central Lymph Metastasis in Papillary Thyroid Carcinoma With Unilateral Lateral Neck Metastasis Using Propensity Score Matching

Kyorim Back
Chung-Ang University Hospital, Chung-Ang University School of Medicine
Ra-Yeong Song
Chung-Ang University Hospital, Chung-Ang University School of Medicine
Jee Soo Kim
Samsung Medical Center, Sungkyunkwan University School of Medicine
Jun-Ho Choe
Samsung Medical Center, Sungkyunkwan University School of Medicine
Yoo Shin Choi
Chung-Ang University Hospital, Chung-Ang University School of Medicine
Jung-Han Kim (jinnee.kim@samsung.com)
Samsung Medical Center, Sungkyunkwan University School of Medicine

Research Article

Keywords: papillary thyroid carcinoma, contralateral central neck metastasis and recurrence, contralateral central neck dissection in clinical or radiological contralateral central node negative patients with unilateral N1b, Bilateral central neck dissection and surgical morbidities

Posted Date: April 26th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-436944/v1

Abstract

This study aimed to evaluate long-term prognosis of contralateral central neck dissection in papillary thyroid cancer (PTC) patients with ipsilateral lateral neck metastasis. We aimed to produce clinical evidence to help determine the extent of central neck dissection (CND) focusing on the separation between the ipsilateral and contralateral sides. A total of 708 PTC patients who underwent total thyroidectomy and concomitant ipsilateral or bilateral CND with ipsilateral lateral neck dissection (LND) were retrospectively included between January 1997 and December 2015 at a single institution. The median follow-up time was 89.7 months, the mean age was 44.7 years and the mean tumor size was 1.5 cm. Among the study population, 507 were female (71.5%) and 201 (28.5%) were male. Locoregional recurrence (LRR) was observed in 26 (7.9%) patients and 30 (7.9%) patients in the ipsilateral and bilateral CND groups, respectively. There were 6 (1.8%) contralateral recurrence cases in the ipsilateral CND group and 5 (1.3%) cases in the bilateral CND group. Male sex (adjusted HR = 1.857, p = 0.034), larger tumor size (adjusted HR = 4.298, p = 0.006), and more metastatic ipsilateral central lymph nodes (adjusted HR = 1.078, p = 0.014) significantly increased the risk of LRR. Ipsilateral CND only did not significantly increase the risk of LRR (adjusted HR = 1.110, p = 0.712). There were no significant differences in recurrence according to contralateral central neck dissection status after propensity score matching (p = 0.424), either. The incidence of hypocalcemia (p = 0.007) was higher in the bilateral CND group compared to the ipsilateral CND group. Surgeons may consider performing contralateral CND only for therapeutic purposes to reduce unnecessary complications.

Synopsis

Ipsilateral CND only did not significantly increase the risk of locoregional recurrence in clinical or radiological contralateral central lymph node negative PTC patients with unilateral lateral neck metastasis. Therefore, Ipsilateral CND only will be sufficient surgical treatment for those patients.

Introduction

Cervical lymph node metastases in papillary thyroid carcinoma (PTC) are quite common[1,2] and are associated with increased locoregional recurrence (LRR)[3–7]. However, PTC has a relatively good prognosis compared to other types of thyroid cancers[8]. For this reason, local recurrence and postoperative quality of life remain important issues. The 2015 ATA guidelines for thyroid cancer management recommend that prophylactic CND (ipsilateral or bilateral) should be considered in clinically involved lateral neck nodes[9], but there is no detailed guideline for the extent of CND with the separation of the ipsilateral or contralateral compartment, and the extent of prophylactic CND depends on the preference of the individual surgeon. To date, there are various studies about the central compartment, however, only a few are about the contralateral central compartment in PTC patients with ipsilateral lateral neck metastasis. Some studies have been conducted to examine contralateral central neck metastasis status and its associated factors but without long-term outcomes dealing with the extent of

CND[6,10]. It is clinically significant to clarify long-term clinical outcomes for contralateral central neck dissection in PTC patients with ipsilateral lateral neck metastasis because of its important role in determining the extent of CND. It is certain that the incidence of surgery-related morbidities, such as hypoparathyroidism or hypocalcemia or VCP, were observed more prominently in bilateral CND compared to ipsilateral CND[11–15]. The purpose of this study was to evaluate the recurrence rate and the risk factors associated with recurrence in accordance with prophylactic contralateral CND. This, in turn, could potentially decrease postoperative morbidities from unnecessary neck dissection.

Methods

Patient selection. This study was approved by the Institutional Review Board at Samsung Medical Center(SMC) and all process were done in accordance with the relevant guidelines and regulations. Informed consent form from all participated patients in this study was obtained. We conducted a retrospective study at a single institution between January 1997 and December 2015. A total of 1,026 patients underwent lateral neck dissection (LND) with concomitant total thyroidectomy at the Thyroid Cancer Center of SMC, a tertiary referral center in Korea. Patients with the following were excluded: preoperative contralateral cN1a patients, a history of previous thyroidectomy, an age younger than 20 years or older than 80 years, non-PTC carcinomas (follicular/medullary/anaplastic), PTC variants, mixed type PTC, LND without thyroidectomy due to lateral neck recurrence, completion thyroidectomy, bilateral LND, distant metastasis, and follow-up duration less than 6 months (residual tumor or suspicious lymph node detected in the bilateral CND group within 6 months after initial surgery or loss to follow-up within 6 months)[16]. Finally, a total of 708 PTC patients who underwent total thyroidectomy with either ipsilateral central neck dissection (CND) + ipsilateral LND or bilateral CND + ipsilateral LND were enrolled (Fig. 1).

All patients were examined by ultrasonography (US) and/or computed tomography (CT) preoperatively to evaluate primary tumor and the presence of suspected nodal metastases. Korean Thyroid Imaging Reporting and Data System(K-TIRADS) by The Korean Society of Thyroid Radiology (KSThR) was used as a guideline for US-based diagnosis. Suspicious lesions were diagnosed by fine needle aspiration (FNA). Suspicious lymph nodes in the lateral compartment were confirmed by FNA or thyroglobulin (Tg) washout measurement. Based on the American Thyroid Association (ATA) Guidelines[9], clinically involved lymph node disease (cN1) was defined as lymph node metastases in the central neck compartment on preoperative imaging[16].

Surgical methods. Surgical strategies were chosen according to the ATA Guidelines[9]. All patients underwent total thyroidectomy with either ipsilateral CND + ipsilateral LND or bilateral CND + ipsilateral LND. Therapeutic contralateral CND was typically performed after central lymph node metastasis was detected during preoperative US or surgery. Patients without contralateral central lymph node metastasis by preoperative exams underwent prophylactic contralateral CND at the discretion of the surgeon. The operations were performed by three endocrine surgeons (A, B, C) in our hospital; surgeon A performed routine bilateral CND and surgeon B and C preferred to perform bilateral CND only if contralateral central

lymph node metastasis was suspected using preoperative images or gross inspection during surgery regardless of pathological contralateral central neck metastasis[16]. Approximately 61% of the patients with bilateral CND were patients who underwent surgery by surgeon A. The rest 39% of the patients with bilateral CND were patients who underwent surgery by surgeon B and C. Thyroditis with CLN enlargement is common in Korean patients who live in an iodine-rich area. Ultrasound features can be diverse depending on the severity of disease in patients with thyroditis. Among the patients who underwent surgery by surgeon B and C, 51% presented with CLT. In addition, our analysis is based on the cohort without radiologically detectable contralateral central lymph node metastasis. The term “ipsilateral” was used to indicate the same side as the main tumor, and “contralateral” was defined as the opposite side relative to the main tumor. In cases of bilateral tumors, the largest tumor was considered to be the main tumor. Ipsilateral central lymph nodes were defined as ipsilateral paratracheal, pretracheal lymph nodes, and precricoid (Delphian) nodes. Lymph nodes in the paratracheal region that were contralateral to the main tumor or opposite to a lateral neck metastasis were defined as contralateral central lymph nodes. LND refers to a lateral neck compartmental lymph node dissection. LND was defined as a neck dissection of levels II–V, conserving the internal jugular vein, spinal accessory nerve, and sternocleidomastoid muscle. Therapeutic LND was performed only in patients with lateral neck metastasis confirmed by FNA preoperatively. LND specimens were separated by the surgeon according to the neck level at the time of surgery[16].

Histopathological examination of surgical specimens. Surgical specimens were microscopically examined by two or more experienced pathologists. The following histopathologic factors were assessed: main tumor size (longest diameter of the largest lesion), cell type of main tumor, multifocality, tumor bilaterality, extrathyroidal extension (ETE; microscopic or gross), regional LN metastasis (central or lateral compartment), and underlying conditions of the thyroid, such as chronic lymphocytic thyroiditis (CLT). The staging of thyroid cancer was determined in accordance with the 7th edition of the AJCC Cancer Staging Manual and the Future of TNM[17].

Surgery-related outcomes. Various surgery-related outcomes were assessed. The terms “transient” and “permanent” were defined on a six-month basis. “Transient” was defined as a symptom duration of less than 6 months and “permanent” was defined as a symptom duration of more than 6 months. Hypocalcemia was defined as a serum calcium < 8.0 mg/dl. Calcium level were the lowest value within or more than six months of surgery accordingly. Recurrent laryngeal nerve injury described as vocal cord palsy (VCP) was diagnosed by laryngoscopy or patient’s symptoms. Postoperative serum thyroglobulin (Tg) level in Table 1 was defined as the stimulated Tg after the first ablation.

Table 1
Clinicopathological characteristics of 708 PTC patients who underwent total thyroidectomy with either ipsilateral CND + ipsilateral LND or bilateral CND + ipsilateral LND.

	Ipsilateral CND	**Bilateral CND**	**p value**
	No. (%)	**No. (%)**	
Total	329 (46.5)	379(53.5)	
Age (yr)			
Mean ± SD	45.1 ± 12.6	44.31 ± 12.5	0.429
< 55	258 (78.4)	307 (81.0)	0.393
≥ 55	71 (21.6)	72 (19.0)	
Sex			0.367
Female	241 (73.3)	266 (70.2)	
Male	88 (26.7)	113 (29.8)	
BMI (kg/m^2)			
Mean ± SD	23.8 ± 3.5	24.0 ± 3.5	0.338
Preoperative ipsilateral cN1a	77 (23.4)	61 (16.1)	0.014
Tumor size (cm)			
Mean ± SD	1.4 ± 1.0	1.5 ± 1.0	0.056
< 1.0	143 (43.5)	134 (35.4)	0.012
1.0–2.0	131 (39.8)	159 (42.0)	
2.0–4.0	48 (14.6)	74 (19.5)	
> 4.0	7 (2.1)	12(3.2)	
Multiplicity			0.004
Absent	221 (67.2)	214 (56.5)	
Present	108 (32.8)	165 (43.5)	
Bilaterality			0.824
Absent	238(72.3)	277 (73.1)	

PTC papillary thyroid carcinoma, *CND* central neck dissection, *LND* lateral neck dissection, *SD* standard deviation, *LN* lymph node, *BMI* Body mass index, *ETE* extrathyroidal extension, *CLT* chronic lymphocytic thyroiditis, *CLN* central lymph node, *CCLN* contralateral central lymph node, *CNM* central neck metastasis, *CCND* contralateral central neck dissection, *CCNM* contralateral central neck metastasis.

	Ipsilateral CND No. (%)	Bilateral CND No. (%)	p value
Present	91(27.7)	102 (26.9)	
Gross ETE			0.824
Absent	290 (88.1)	332 (87.6)	
Present	39 (11.9)	47 (12.4)	
Number of Retrieved CLNs	10.3 ± 12.6	16.0 ± 19.2	< 0.001
Number of Metastatic ipsilateral CLNs	2.8 ± 4.1	3.8 ± 3.2	0.001
Number of Metastatic CCLNs	N/A	2.5 ± 2.0 (1–10)	*N/A*
Number of Retrieved LLNs	25.9 ± 13.5	37.6 ± 13.9	< 0.001
Number of Metastatic LLNs	7.5 ± 10.1	5.8 ± 4.0	0.007
Ipsilateral CNM	245 (74.5)	318 (83.9)	0.002
Contralateral CNM	0 (0.0)	131(34.6)	*N/A*
Radioactive iodine therapy			< 0.001
Yes	310 (94.2)	379 (100)	
No	19 (5.8)	0 (0.0)	
Radioactive iodine, mCi, mean ± SD	117.6 ± 80.0	142.2 ± 67.6	< 0.001
Stimulated serum Tg after ablation	1.97 ± 2.4	1.28 ± 2.0	< 0.001
Overall Recurrence	26 (7.9)	30 (7.9)	0.995
Contralateral recurrence	4 (1.2)	4 (1.1)	1.000

PTC papillary thyroid carcinoma, *CND* central neck dissection, *LND* lateral neck dissection, *SD* standard deviation, *LN* lymph node, *BMI* Body mass index, *ETE* extrathyroidal extension, *CLT* chronic lymphocytic thyroiditis, *CLN* central lymph node, *CCLN* contralateral central lymph node, *CNM* central neck metastasis, *CCND* contralateral central neck dissection, *CCNM* contralateral central neck metastasis.

Postoperative follow-up and management. After the initial surgery, all patients underwent regular follow-up at 6- to 12-month intervals with clinical evaluations including physical examinations, US, CT, Iodine-131 (^{131}I) scans, and serum unstimulated Tg level. Suspicious lesions for recurrence were confirmed by US-guided FNA biopsy with or without Tg washout level and/or CT or positron emission tomography (PET). Locoregional recurrence was defined as the presence of tumors or metastatic lymph nodes on cytology from FNA. Radioactive iodine (RAI) therapy was performed with ^{131}I at 4–12 weeks after surgery according to the ATA guidelines[9]. RAI was administered after thyroid hormone withdrawal or after

stimulation with recombinant thyroid-stimulating hormone. When RAI treatment was no longer required, patients resumed regular follow-up. The last date of follow-up was defined as loss to follow-up, withdrawal, recurrence, or death. In this study, all patients received postoperative RAI therapy, and TSH suppression was performed according to the ATA guidelines[9].

Statistical analysis. Statistical analyses were performed using SPSS version 22.0 software (IBM Corp, Armonk, NY, USA), and statistically significant differences were defined as *P*-values less than 0.05. Continuous variables are presented as mean ± standard deviation (SD), and categorical variables are presented as the number with percentage (%) and odds ratio (OR). The chi-square test and linear-by-linear association were used for categorical variables and the Student's *t*-test for continuous variables. For recurrence analysis, Cox regression was used to determine if the clinicopathological characteristics were associated with contralateral CND in patients with PTC. Propensity score matching was performed to adjust clinicopathological variables which can effect on recurrence. Under the matched condition, Kaplan-Meier and the log-rank test were adopted to analyze time-dependent LRR.

Results

Clinicopathological characteristics of 708 PTC patients who underwent total thyroidectomy with either ipsilateral CND + ipsilateral LND or bilateral CND + ipsilateral LND. The mean patient age was 44.7 years (range, 20–77) and the mean tumor size was 1.5 cm (range, 0.1–8). Among the study population, 507 were female (71.5%) and 201 (28.5%) were male. Of the 708 patients, 329 (46.5%) underwent ipsilateral CND and 379 (53.5%) patients underwent bilateral CND. Tumor multiplicity was seen in 108 (32.8%) patients in the ipsilateral CND group and 165 (43.5%) patients in the bilateral CND group. Tumor bilaterality was found in 91 (27.7%) patients in the ipsilateral CND group and 102 (26.9%) patients in the bilateral CND group. Gross ETE was observed in 39 (11.9%) patients in the ipsilateral CND group and 47 (12.4%) patients in the bilateral CND group. In the bilateral CND group of 379 patients, contralateral central neck metastasis occurred in 131 (34.6%) patients. Of the 33 patients with tumor encroaching on isthmus, there were 23 (69.7%) patients who underwent bilateral CND; 13 (39.4%) patients had contralateral central lymph node metastasis and 10 (30.3%) patients had no contralateral central lymph node metastasis. The final 10 (30.3%) patients with tumor encroaching on isthmus were in the ipsilateral CND group. For RAI therapy, most patients in the whole cohort received RAI treatment except for the 19 (5.8%) patients in the ipsilateral CND group.

A comparison of the two groups showed that preoperative ipsilateral cN1a ($p = 0.014$), tumor multiplicity in a single lobe ($p = 0.004$), a number of retrieved central lymph nodes (CLN) ($p < 0.001$), number of metastatic ipsilateral CLNs ($p = 0.001$), a number of retrieved lateral lymph nodes (LLN) ($p < 0.001$), a number of metastatic LLNs ($p = 0.007$), ipsilateral central neck metastasis (CNM) ($p = 0.002$), RAI treatment status ($p < 0.001$), RAI dose difference ($p < 0.001$), and post-operative stimulated Tg level ($p < 0.001$) were significantly different (Table 1). Recurrence ($p = 0.995$) and contralateral recurrence ($p = 1.000$) were not statistically different between the two groups. LRR was observed in 26 (7.9%) patients in the ipsilateral CND group and 30 (7.9%) patients in the bilateral CND group. Contralateral recurrence

occurred in 8 patients in the whole cohort; there were 4 (1.2%) contralateral recurrence cases in the ipsilateral CND group and 4 (1.1%) cases in the bilateral CND group (Table 1).

Recurrence sites for 56 recurred patients. There were 56 (7.9%) recurred patients in the whole population. Among 26 (7.9%) patients with LRR in the ipsilateral CND group, recurrence was detected at the ipsilateral thyroidectomy site in 1 (0.3%) patient, ipsilateral central neck in 5 (1.5%) patients, and ipsilateral lateral neck in 11 (3.3%) patients. Contralateral recurrence occurred in 6 patients overall: 1 (0.3%) cases in the contralateral lateral neck, 1 (0.3%) case in the ipsilateral thyroidectomy site + contralateral central neck, 1 (0.3%) case in the contralateral thyroidectomy site + contralateral lateral neck, and 1 (0.3%) case in the ipsilateral thyroidectomy site + contralateral central and lateral neck. In addition, 2 (0.6%) bilateral lateral neck metastasis cases were also observed (Table 2).

Table 2
Recurrence sites of 56 (7.9%) recurred patients who underwent total thyroidectomy with either ipsilateral CND. + ipsilateral LND or bilateral CND + ipsilateral LND.

Recurrence site	**Ipsilateral CND (n = 329) No. (%)**	**Bilateral CND (n = 379) No. (%)**
Total	26 (7.9)	30 (7.9)
Ipsilateral thyroidectomy site	1 (0.3)	6 (1.6)
Contralateral thyroidectomy site	0 (0.0)	1 (0.3)
Ipsilateral central neck	5 (1.5)	2 (0.5)
Contralateral central neck	0 (0.0)	0 (0.0)
Ipsilateral lateral neck	11 (3.3)	18 (4.8)
Contralateral lateral neck	1 (0.3)	3 (0.8)
Bilateral lateral neck	2 (0.6)	
Ipsilateral thyroidectomy site + Ipsilateral central neck	2 (0.6)	
Ipsilateral thyroidectomy site + contralateral central neck	1 (0.3)	
Ipsilateral thyroidectomy site + ipsilateral lateral neck		
Contralateral thyroidectomy site + contralateral lateral neck	1 (0.3)	
Ipsilateral thyroidectomy site + contralateral central and lateral neck	1 (0.3)	
Ipsilateral central neck + ipsilateral lateral neck	1 (0.3)	

CND central neck dissection, *LND* lateral neck dissection, *CCNM* contralateral central neck metastasis.

In the bilateral CND group, there were 30 (7.9%) patients with LRR. Recurrence occurred at the ipsilateral thyroidectomy site in 6 (1.6%) patients, contralateral thyroidectomy site in 1 (0.3%) patients, ipsilateral central neck in 2 (0.5%) patients, and ipsilateral lateral neck in 18 (4.8%) patients. Contralateral recurrence occurred in 4 patients overall; there were 1 (0.3%) case in the contralateral thyroidectomy site, 3 (0.8%) cases in the contralateral lateral neck. There was no contralateral central neck recurrence in either groups (Table 2).

Prognostic impact of node dissection status on locoregional recurrence in 708 PTC patients. The median follow-up time was 89.7 months (range, 7–212 months). After adjustment for clinicopathological characteristics in the Cox proportional hazard model, male sex (adjusted HR = 1.857, p = 0.034), larger tumor size (adjusted HR = 4.298, p = 0.006), and greater number of metastatic ipsilateral CLNs (adjusted HR = 1.078, p = 0.014) significantly increased the risk of LRR. It was shown that ipsilateral CND only did not significantly increased the risk of LRR (adjusted HR = 1.110, p = 0.712) (Table 3).

Table 3
Cox proportional-hazards analysis to identify risk factors for loco-regional recurrence in 708 PTC patients after adjustment various conditions.

	Loco-regional recurrence	
	Adjusted HR (95 % CI)[a]	**p value**
Age < 55 years	1.000 (0.506–1.929)	0.971
Male sex	1.857 (1.049–3.289)	0.034
Tumor Size		0.003
≤ 1.0	*Ref*	*Ref*
1.0–2.0	0.794(0.400-1.587)	0.514
2.0–4.0	2.056(1.032–4.096)	0.040
> 4.0	4.298(1.533–12.051)	0.006
Gross ETE (*Ref = absent*)	1.297 (0.598–2.809)	0.510
CLT (*Ref = absent*)	0.930 (0.464–1.866)	0.839
Multiplicity (*Ref = absent*)	1.117 (0.604–2.065)	0.725
Bilaterality (*Ref = absent*)	0.773 (0.390–1.531)	0.460
Ipsilateral CND (*Ref = Biilateral CND*)	1.110 (0.638–1.931)	0.712
Number of Metastatic ipsilateral CLNs	1.078 (1.016–1.144)	0.014
Radioactive iodine	1.000(0.997–1.003)	0.923

PTC papillary thyroid carcinoma, *HR* hazard ratio, *CI* confidence interval, *ETE* extrathyroidal extension, *CLT* chronic lymphocytic thyroiditis, *LN* lymph node, *CNM* central neck metastasis, *CND* central neck dissection, *Ref* reference.

[a]Adjusted for sex, age < 55 years, tumor size, gross ETE, CLT, multiplicity, bilaterality, Number of Metastatic CLNs, RAI dose.

Prognostic impact of contralateral central node dissection status on locoregional recurrence in 706 PTC patients after propensity score matching. Propensity Score matching was performed to compare “contralateral central node dissection” with “no contralateral central node dissection”. Before propensity score matching, tumor size (p = 0.012), multifocality (p = 0.004) were more frequently observed in contralateral central neck dissection group. The patients who underwent contralateral central neck dissection received relatively higher dose RAI (117.6 mCi vs 142.2 mCi, p < 0.001) (Table 4). After propensity matching, there were 130 matched pairs. There was no significant difference in patients’ characteristics between two groups and loco-regional recurrence was analyzed. The median follow-up time was 93.7 months (range, 6– 212 months). Of 11 recurred patients, 8(6.2%) and 3(2.3%) patients were in CCND (-) group and CCND (+) group, respectively. Recurrence-free survival rates in either

ipsilateral or bilateral CND groups were 97.8% versus 97.6% at 5 years, 75.5% versus 97.6% at 10 years, respectively (p = 0.424) (Fig. 2). Furthermore, the recurrence-free survival rates for overall contralateral recurrence, including thyroidectomy site, central or lateral neck, in the ipsilateral or bilateral CND groups were 100.0% versus 99.2% at 5 years, 86.8% versus 99.2% at 10 years, respectively (p = 0.609) (Fig. 3). There were no statistically significant differences in RFS rates according to contralateral central neck dissection status.

Table 4
Clinicopathological characteristics according to contralateral central lymph node dissection status before and after propensity score matching.

	Before propensity score matching			After propensity score matching		
	CCND (-) N (%)	CCND (+) N (%)	p value	CCND (-) N (%)	CCND (+) N (%)	p value
Total	329 (46.5)	379 (53.5)	*N/A*	130 (50.0)	130 (50.0)	*N/A*
Age (yr)			0.393			1.000
< 55	258 (78.4)	307 (81.0)		115 (88.5)	115 (88.5)	
≥ 55	71 (21.6)	72 (19.0)		15 (11.5)	15 (11.5)	
Sex			0.367			1.000
Female	241 (73.3)	266 (70.2)		104 (80.0)	104 (80.0)	
Male	88 (26.7)	113 (29.8)		105 (20.0)	160 (20.0)	
Tumor size (cm)			0.012			1.000
≤ 1.0	143 (43.5)	134 (35.4)		50 (38.5)	50 (38.5)	
1.0–2.0	131 (39.8)	159 (42.0)		67 (51.5)	67 (51.5)	
2.0–4.0	48 (14.6)	74 (19.5)		12 (9.2)	12 (9.2)	
> 4.0	7 (2.1)	12 (3.2)		1 (0.8)	1 (0.8)	
Gross ETE			0.824			1.000
Absent	290 (88.1)	332 (87.6)		124 (95.4)	124 (95.4)	
Present	39 (11.9)	47 (12.4)		6 (4.6)	6 (4.6)	
CLT			0.081			1.000
Absent	259 (78.7)	277 (73.1)		108 (83.1)	108 (83.1)	
Present	70 (21.3)	102 (26.9)		22 (16.9)	22 (16.9)	
Multifocality			0.004			1.000
Absent	221 (67.2)	214 (56.5)		82 (63.1)	82 (63.1)	
Present	108 (32.8)	165 (43.5)		48 (36.9)	48 (36.9)	
Bilaterality			0.824			1.000
Absent	238 (72.3)	277 (73.1)		101 (77.7)	101 (77.7)	

ETE extrathyroidal extension, *CLT* chronic lymphocytic thyroiditis, *CND* central neck dissection, *CCND* contralateral central neck dissection, RAI radioactive iodine therapy, *N/A* not available, *Ref* reference.

	Before propensity score matching			After propensity score matching		
	CCND (-) N (%)	CCND (+) N (%)	p value	CCND (-) N (%)	CCND (+) N (%)	p value
Present	91 (27.7)	102 (26.9)		29 (22.3)	29 (22.3)	
RAI (mCi)			< 0.001			1.000
dose	117.6 ± 79.9	142.2 ± 67.6		124.5 ± 46.9	124.5 ± 46.9	

ETE extrathyroidal extension, *CLT* chronic lymphocytic thyroiditis, *CND* central neck dissection, *CCND* contralateral central neck dissection, RAI radioactive iodine therapy, *N/A* not available, *Ref* reference.

Surgery-related outcomes in 706 PTC patients according to contralateral CND status. Hospital days (5.37 days vs 5.31 days; p = 0.814), postoperative days (4.04 days vs 4.21 days; p = 0.302), total drainage (234 mL vs 273 mL; p = 0.320), VCP (0.0% vs 0.3%; p = 1.000), postoperative bleeding (0.6% vs 0.5%; p = 1.000), chyle leak (1.8% vs 1.3%; p = 0.280), and wound infection were not different between the ipsilateral CND and bilateral CND groups. However, the incidence of hypocalcemia (4.0% vs 7.1%; p = 0.007) was significantly higher in the bilateral CND group and operation time (170.4 min vs 220.3 min, p < 0.001) were longer in the bilateral CND group compared to the ipsilateral CND group (Table 5).

Table 5
Comparison of surgical outcomes according to extent of central neck dissection in patients who underwent total thyroidectomy with either ipsilateral CND + ipsilateral LND or bilateral CND + ipsilateral LND.

Total (n = 708)	Ipsilateral CND (n = 329) No. (%)	Bilateral CND (n = 379) No. (%)	p value
Hospital days			
Mean ± SD	5.37 ± 3.976	5.31 ± 2.382	0.814
Postoperative days			
Mean ± SD	4.04 ± 2.427	4.21 ± 1.555	0.302
Operation time (min)			
Mean ± SD	170.41 ± 51.66	220.32 ± 52.32	< 0.001
Total drainage (mL)			
Mean ± SD	234.03 ± 56.37	273.35 ± 51.38	0.320
Hypocalcemia	13 (4.0)	27 (7.1)	0.007
Vocal cord palsy	0(0.0)	1(0.3)	1.000
Wound infection	0(0.0)	0(0.0)	N/A
Bleeding	2 (0.6)	2 (0.5)	1.000
Chyle leakage	6 (1.8)	5 (1.3)	0.280

CND central neck dissection, *SD*, standard deviation.

Discussion

Previous studies have reported that the rate of regional lymph node metastasis in patients with PTC is approximately 30% up to 80%[18,19] and central lymph node metastasis is already present in 40–60% of patients at the time of diagnosis[20–22]. Other studies demonstrated that the rate of contralateral central neck metastasis in patients with ipsilateral lateral neck metastasis was 34.7% and 5–30% in the final pathology, respectively[23,24]. Since these rates were relatively high, there has been a controversy as to whether or not surgeons should perform contralateral central neck dissection (CND) without suspicious contralateral central lymph nodes on preoperative imaging. In addition, there have not been many studies on this subject to date, therefore the long term effect of prophylactic contralateral CND in PTC patients with ipsilateral lateral neck metastasis are still unclear. To the best of our knowledge, this study is one of the few studies to investigate the long-term outcome of prophylactic contralateral central neck dissection in PTC patients with ipsilateral lateral neck metastasis.

In our study, male sex, larger tumor size, and greater number of metastatic ipsilateral CLNs significantly increased the risk of LRR, however, ipsilateral CND only did not increase the risk of recurrence (Tables 3

and 4, Figs. 2 and 3). In the ipsilateral CND group, the rate of recurrence in the ipsilateral central or lateral neck was higher than those in the contralateral central or lateral neck (Table 2). There was no significant difference in recurrence regarding CND status with either the ipsilateral or bilateral sides (Figs. 2 and 3).

The point is, recurrence is more likely to occur in the ipsilateral neck, not in the contralateral central neck or lateral neck in this whole study population (Table 2). A previous study reported by Oshima et al. demonstrated that male sex, larger tumor size, ETE, and gross nodal metastasis were associated factors for contralateral lateral neck recurrence[25]. However, contralateral neck recurrence rarely occurred so it was difficult to analyze risk factors for contralateral recurrence in our study.

Based on our results, we found that ipsilateral CND only was not associated with a higher risk of either overall recurrence or contralateral recurrence. Interestingly, there was no tumor recurrence in the contralateral central neck among the whole study population, regardless of whether bilateral CND was performed. LRR occurred mostly in the ipsilateral thyroidectomy site and/or ipsilateral compartment.

Some studies concluded that microscopic node metastasis occurs frequently, but it does not give rise to the higher recurrence risk seen in clinically detectable macroscopic disease[26,27]. Randolph et al. reported that microscopic lymph node metastasis appeared to be present in up to 80% of patients, but recurrence rates ranged from 2–6%[26]. Our study showed that microscopic central neck metastasis was present in 68.5% of patients, and recurrence rate was 7.9%. Hughes DT et al. concluded that there was no significant difference in postoperative Tg level between the thyroidectomy alone group and prophylactic CND group in pathologic N1a patients who presented preoperatively cN0[27]. On the other hand, even if there's a difference in study population, this study found that Tg was higher in the ipsilateral CND group than in the bilateral CND group with no difference in overall recurrence.

The prevalence of contralateral central neck metastasis in our study was 37.8% (150/397) of patients with ipsilateral lateral neck metastasis. Out of theses 150 patients, preoperative contralateral cN1a was found in only 20 (13.3%) patients, implying that most contralateral central lymph node metastasis is microscopic metastasis. Preoperative contralateral cN1a was not commonly found in PTC patients with ipsilateral lateral neck metastasis (N1b) and we were not even able to ensure that contralateral cN1a increased the likelihood of LRR as well as microscopic contralateral central neck metastasis from this study.

Postoperative complications such as hypocalcemia were higher in patients who underwent bilateral CND than those who underwent ipsilateral CND (Table 4). This is a critical issue in thyroid surgery because hypocalcemia is closely associated with the patients' quality of life, and all endocrine surgeons should not ignore it.

Given the results above, prophylactic contralateral CND may not be necessary in patients with ipsilateral cN1b as a routine procedure. These retrospective data suggest that PTC patients with ipsilateral N1b presenting with evident lymphadenopathy intraoperatively or on preoperative imaging in the contralateral central compartment should undergo therapeutic contralateral CND. Unless there is an evident

contralateral metastatic lymph node preoperatively or a detectable contralateral cN1a intraoperatively, ipsilateral CND may be sufficient surgical treatment of the PTC patients with ipsilateral N1b.

This study had several limitations. First, our study was a non-randomized, retrospective, cohort study. Confounding variables or unmeasured factors may not have been identified, and there was possible surgeon bias in the decision to undergo ipsilateral CND versus bilateral CND. That is, the whole cohort was not treated in a random fashion. Thus, further prospective, randomized trials are needed to resolve this selection bias issue in order to clearly compare recurrence rates between the ipsilateral CND and bilateral CND groups. Second, a longer follow-up period is required to assess recurrence and survival more completely. Third, inter-observer variation in the detection and interpretation of cervical lymph node metastasis and inconsistent surgical management were involved because of the long-term period of data collection. Fourth, our findings may not be applicable to smaller centers without a skilled team such as high volume surgeons or radiologists since the experts' factor could contribute to the low incidence of recurrence and contralateral recurrence. Performing prophylactic contralateral CND may rather decrease recurrence and help postoperative treatment planning and follow-up in small institutions with less skill in preoperative node evaluation; even this may demonstrate higher microscopic nodal disease. Despite these limitations, this study still has the value of a retrospective study in examining the role of CND in PTC as a prospective randomized trial may not easily feasible[28]. By analyzing adequate sample size in a single institution, we tried to minimize inadequate statistical power and local institutional variability using specific inclusion factors and follow-up.

In conclusion, This study suggests that bilateral central neck dissection increased surgery-related complications, especially hypocalcemia, and may not reduce the risk of recurrence in PTC patients with unilateral N1b; therefore, surgeons may perform contralateral CND only in the presence of clinically evident or suspected nodal disease.

Declarations

Funding Support

This work had no specific funding.

Author Disclosure Statement

The authors have no conflicts of interest to declare.

Author contributions

Kyorim Back and Jung-Han Kim have set up and conducted the experiment. Jee Soo Kim, Jun-Ho Choe and Jung-Han Kim contributed to thyroid operation and diagnostics development. Kyorim Back analyzed the data, and Ra-Yeong Song and Yoo Shin Choi prepared the figures. Kyorim Back wrote the manuscript.

Jee Soo Kim, Jun-Ho Choe and Jung-Han Kim supervised the project. All authors reviewed the manuscript and contributed to discussions

Competing interests

The author(s) declare no competing interests

References

1. Grebe, S. K. & Hay, I. D. Thyroid cancer nodal metastases: biologic significance and therapeutic considerations. *Surg. Oncol. Clin. N. Am.* **5**, 43–63 (1996).
2. Kouvaraki, M. A. *et al.* Role of preoperative ultrasonography in the surgical management of patients with thyroid cancer. *Surgery.* **134**, 946–954 discussion 954 – 945 https://doi.org/10.1016/s0039-6060(03)00424-0 (2003).
3. Leboulleux, S. *et al.* Prognostic factors for persistent or recurrent disease of papillary thyroid carcinoma with neck lymph node metastases and/or tumor extension beyond the thyroid capsule at initial diagnosis. *J. Clin. Endocrinol. Metab.* **90**, 5723–5729 https://doi.org/10.1210/jc.2005-0285 (2005).
4. Lundgren, C. I., Hall, P., Dickman, P. W. & Zedenius, J. Clinically significant prognostic factors for differentiated thyroid carcinoma: a population-based, nested case-control study. *Cancer.* **106**, 524–531 https://doi.org/10.1002/cncr.21653 (2006).
5. Mazzaferri, E. L. & Jhiang, S. M. Long-term impact of initial surgical and medical therapy on papillary and follicular thyroid cancer. *Am. J. Med.* **97**, 418–428 https://doi.org/10.1016/0002-9343(94)90321-2 (1994).
6. Roh, J. L., Kim, J. M. & Park, C. I. Lateral cervical lymph node metastases from papillary thyroid carcinoma: pattern of nodal metastases and optimal strategy for neck dissection. *Ann. Surg. Oncol.* **15**, 1177–1182 https://doi.org/10.1245/s10434-008-9813-5 (2008).
7. Conzo, G. *et al.* Predictive value of nodal metastases on local recurrence in the management of differentiated thyroid cancer. Retrospective clinical study. *BMC Surg.* **13 Suppl 2**, S3, http://doi.org/10.1186/1471-2482-13-S2-S3 (2013).
8. Siegel, R. *et al.* Cancer treatment and survivorship statistics, 2012. *CA Cancer J. Clin.* **62**, 220–241 https://doi.org/10.3322/caac.21149 (2012).
9. Haugen, B. R. *et al.* 2015 American Thyroid Association Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer: The American Thyroid Association Guidelines Task Force on Thyroid Nodules and Differentiated Thyroid Cancer. *Thyroid* **26**, 1-133, http://doi.org/10.1089/thy.2015.0020 (2016).
10. Koo, B. S., Choi, E. C., Park, Y. H., Kim, E. H. & Lim, Y. C. Occult contralateral central lymph node metastases in papillary thyroid carcinoma with unilateral lymph node metastasis in the lateral neck. *J. Am. Coll. Surg.* **210**, 895–900 https://doi.org/10.1016/j.jamcollsurg.2010.01.037 (2010).

11. Son, Y. I. *et al.* Extent of prophylactic lymph node dissection in the central neck area of the patients with papillary thyroid carcinoma: comparison of limited versus comprehensive lymph node dissection in a 2-year safety study. *Ann. Surg. Oncol.* **15**, 2020–2026 https://doi.org/10.1245/s10434-008-9928-8 (2008).
12. Mazzaferri, E. L., Doherty, G. M. & Steward, D. L. The pros and cons of prophylactic central compartment lymph node dissection for papillary thyroid carcinoma. *Thyroid.* **19**, 683–689 https://doi.org/10.1089/thy.2009.1578 (2009).
13. Popadich, A. *et al.* A multicenter cohort study of total thyroidectomy and routine central lymph node dissection for cN0 papillary thyroid cancer. *Surgery.* **150**, 1048–1057 https://doi.org/10.1016/j.surg.2011.09.003 (2011).
14. Bergamaschi, R., Becouarn, G., Ronceray, J. & Arnaud, J. P. Morbidity of thyroid surgery. *Am. J. Surg.* **176**, 71–75 https://doi.org/10.1016/s0002-9610(98)00099-3 (1998).
15. Viola, D. *et al.* Prophylactic central compartment lymph node dissection in papillary thyroid carcinoma: clinical implications derived from the first prospective randomized controlled single institution study. *J. Clin. Endocrinol. Metab.* **100**, 1316–1324 https://doi.org/10.1210/jc.2014-3825 (2015).
16. Back, K., Choe, J. H., Kim, J. S. & Kim, J. H. Occult contralateral central neck metastasis in papillary thyroid carcinoma with preoperatively documented ipsilateral lateral neck metastasis. *Eur. J. Surg. Oncol.* https://doi.org/10.1016/j.ejso.2021.01.008 (2021).
17. Edge, S. B. & Compton, C. C. The American Joint Committee on Cancer: the 7th edition of the AJCC cancer staging manual and the future of TNM. *Ann. Surg. Oncol.* **17**, 1471–1474 https://doi.org/10.1245/s10434-010-0985-4 (2010).
18. Liu, X. *et al.* Evolutionary features of thyroid cancer in patients with thyroidectomies from 2008 to 2013 in China. *Sci. Rep.* **6**, 28414 https://doi.org/10.1038/srep28414 (2016).
19. Jeon, M. J. *et al.* Recent Changes in the Clinical Outcome of Papillary Thyroid Carcinoma With Cervical Lymph Node Metastasis. *J Clin Endocrinol Metab.* **100**, 3470–3477 https://doi.org/10.1210/JC.2015-2084 (2015).
20. Pereira, J. A. *et al.* Nodal yield, morbidity, and recurrence after central neck dissection for papillary thyroid carcinoma. *Surgery.* **138**, 1095–1100 discussion 1100 – 1091 https://doi.org/10.1016/j.surg.2005.09.013 (2005).
21. Roh, J. L., Kim, J. M. & Park, C. I. Central lymph node metastasis of unilateral papillary thyroid carcinoma: patterns and factors predictive of nodal metastasis, morbidity, and recurrence. *Ann. Surg. Oncol.* **18**, 2245–2250 https://doi.org/10.1245/s10434-011-1600-z (2011).
22. Moo, T. A. *et al.* Impact of prophylactic central neck lymph node dissection on early recurrence in papillary thyroid carcinoma. *World J. Surg.* **34**, 1187–1191 https://doi.org/10.1007/s00268-010-0418-3 (2010).
23. Mirallie, E. *et al.* Localization of cervical node metastasis of papillary thyroid carcinoma. *World J. Surg.* **23**, 970–973 discussion 973–974 https://doi.org/10.1007/s002689900609 (1999).

24. Machens, A., Hinze, R., Thomusch, O. & Dralle, H. Pattern of nodal metastasis for primary and reoperative thyroid cancer. *World J. Surg.* **26**, 22–28 https://doi.org/10.1007/s00268-001-0176-3 (2002).
25. Ohshima, A. *et al.* Indications for bilateral modified radical neck dissection in patients with papillary carcinoma of the thyroid. *Arch. Surg.* **135**, 1194–1198 discussion 1199 https://doi.org/10.1001/archsurg.135.10.1194 (2000).
26. Randolph, G. W. *et al.* The prognostic significance of nodal metastases from papillary thyroid carcinoma can be stratified based on the size and number of metastatic lymph nodes, as well as the presence of extranodal extension. *Thyroid.* **22**, 1144–1152 https://doi.org/10.1089/thy.2012.0043 (2012).
27. Hughes, D. T. *et al.* Influence of prophylactic central lymph node dissection on postoperative thyroglobulin levels and radioiodine treatment in papillary thyroid cancer. *Surgery.* **148**, 1100–1106 discussion 1006–1107 https://doi.org/10.1016/j.surg.2010.09.019 (2010).
28. Carling, T. *et al.* American Thyroid Association design and feasibility of a prospective randomized controlled trial of prophylactic central lymph node dissection for papillary thyroid carcinoma. *Thyroid.* **22**, 237–244 https://doi.org/10.1089/thy.2011.0317 (2012).

Figures

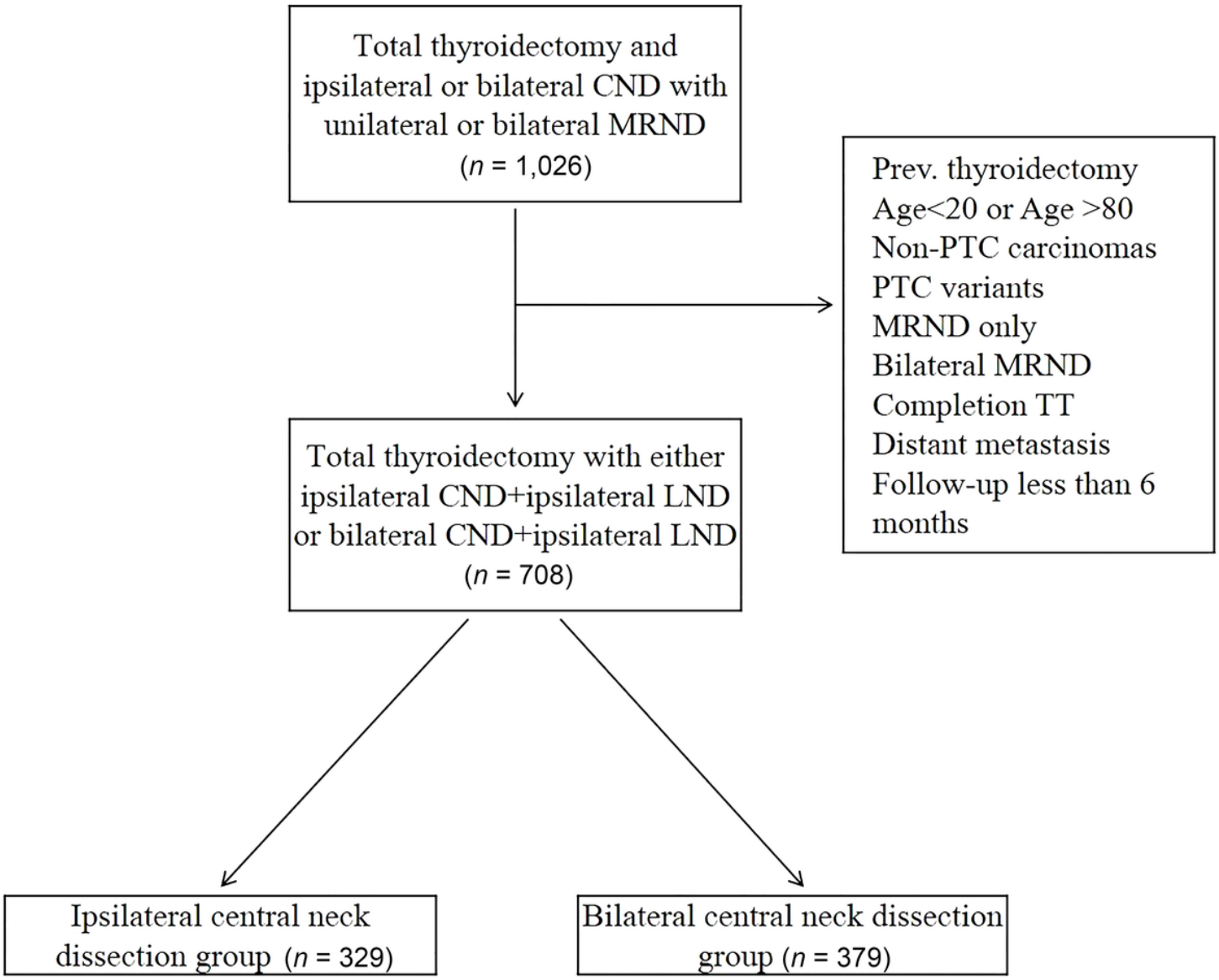

Figure 1

Flow chart of the study population.

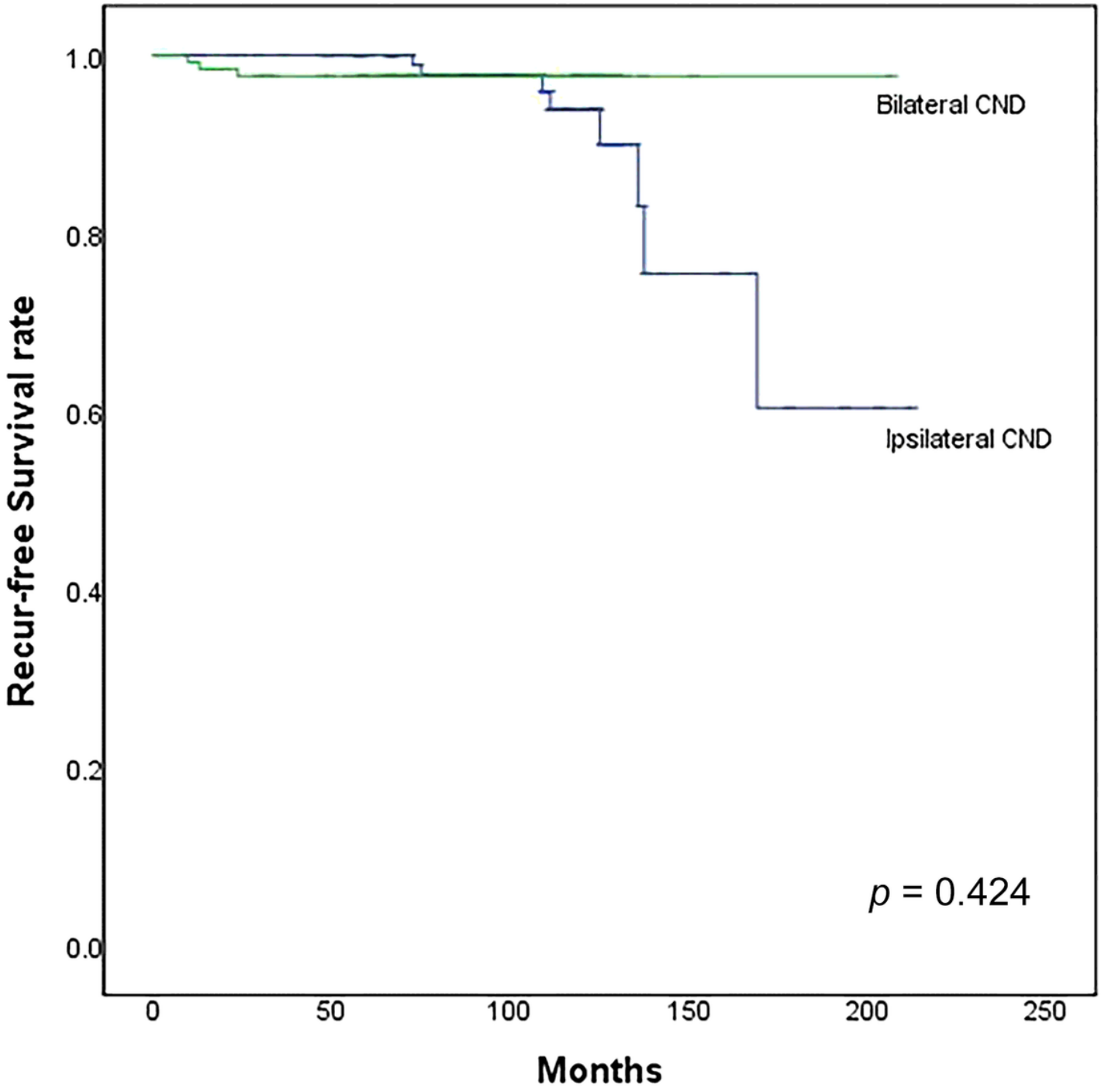

Figure 2

Recurrence-free survival rate for patients with ipsilateral lateral neck metastasis according to the extent of central neck dissection after propensity score matching.

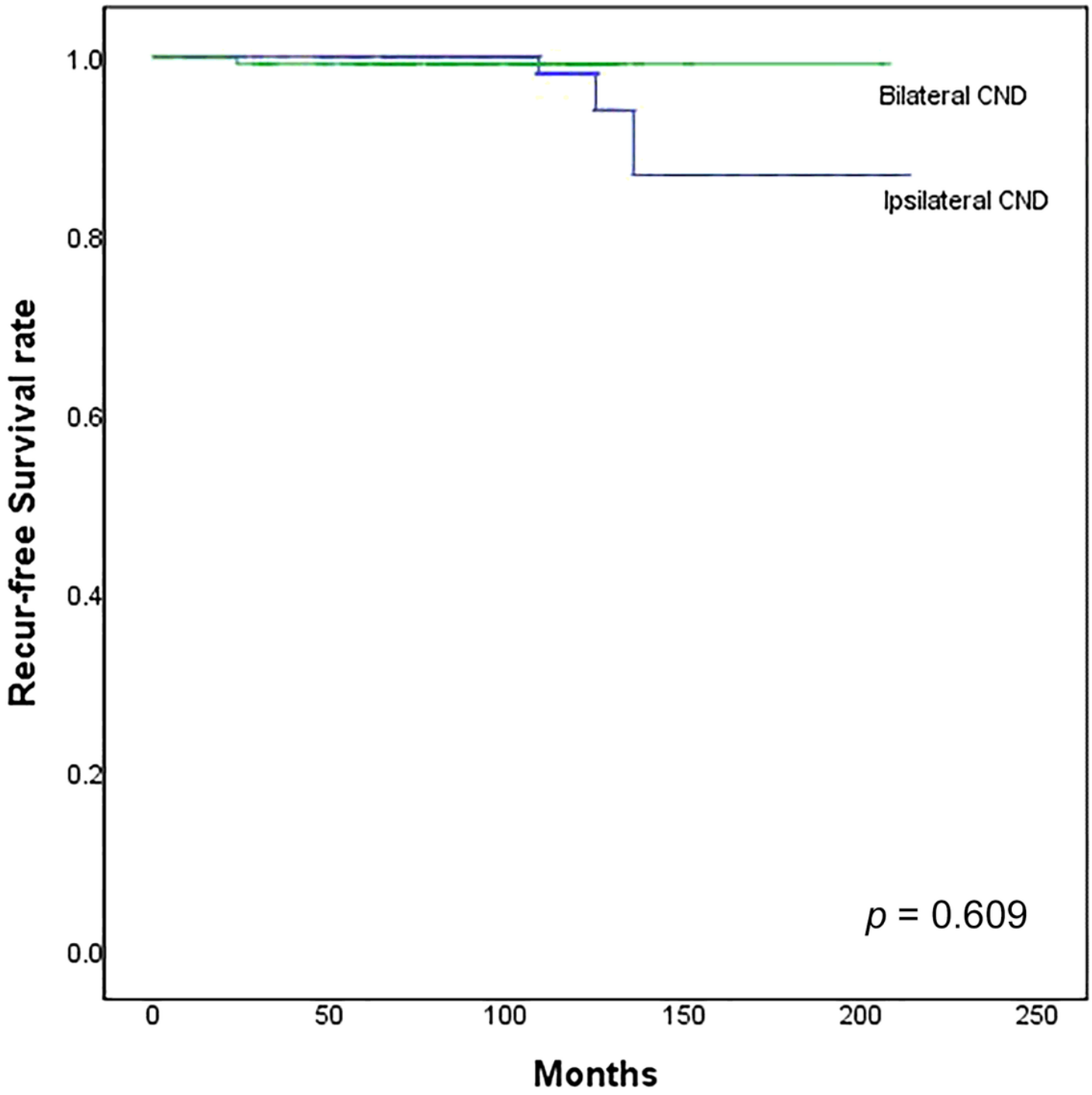

Figure 3

Contralateral recurrence-free survival rate for patients with ipsilateral lateral neck metastasis according to the extent of central neck dissection after propensity score matching.