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The Role of Prophylactic Central Neck Dissection in Clinically Node-Negative T3/T4 Papillary Thyroid Carcinoma

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임상적 전이가 없는 T3, T4 갑상선 유두암 환자에서의 예방적 중심 경부 림프절 절제술 역할

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Background and Objectives The necessity of prophylactic central neck dissection (pCND) in papillary thyroid carcinoma (PTC) remains controversial. This study aimed to investigate the significance of pCND in T3/T4 PTC and evaluate its impact on recurrence and postoperative complications.
Subjects and Method We retrospectively analyzed 1050 patients with clinically node-negative (cN0) PTC who underwent total thyroidectomy with or without pCND between 1995 and 2022. Occult lymph node metastasis, recurrence, and postoperative complications were evaluated. Among the patients, 950 had the T1/T2 disease and 100 had the T3/T4 disease. pCND was performed in 78.9% of the T1/T2 group and 83.0% of the T3/T4 group.
Results Among patients who underwent pCND, occult lymph node metastasis was identified in 37.1% of the T1/T2 group and 43.4% of the T3/T4 group, without significant differences. In both cN0 T1–T4 cohort and the cN0 T3/T4 subgroup, the multivariate Cox regression analysis showed that pCND was not associated with recurrence. In the cN0 T3/T4 group, recurrence occurred in four patients who underwent pCND (4.8%) and in one patient who did not (5.9%), showing no significant difference. There was no central lymph node recurrence; all recurrences observed occurred in the lateral lymph nodes. Transient hypoparathyroidism was significantly higher in the pCND group (p=0.015), but there was no significant difference found in the recurrent laryngeal nerve palsy.
Conclusion The role of pCND may be limited even in cN0 T3/T4 PTC. Recurrence rates did not differ significantly according to pCND, while transient hypoparathyroidism occurred more frequently in the pCND group. Korean J Otorhinolaryngol-Head Neck Surg 2026;69(8):371-80

Keywords Lymph node; Lymphatic metastasis; Neck dissection; Papillary thyroid cancer; Recurrence.

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Introduction

Thyroid papillary carcinoma accounts for the majority of thyroid malignancies and is generally associated with a favorable prognosis. Despite the excellent long-term survival rates in papillary thyroid carcinoma (PTC), cervical lymph node metastasis is common, with reported rates ranging from approximately 20% to 90% depending on tumor size and the characteristics of the study population.[1] The most common site of metastasis is the central lymph node compartment, which is generally associated with a less favorable prognosis,[2,3] as

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reflected in the American Joint Committee on Cancer (AJCC) 8th edition staging system.[4] Most surgeon agree that the patients with clinically suspicious lymph node metastasis should undergo therapeutic central compartment neck dissection in addition to thyroidectomy.

In addition, microscopic metastasis in the central lymph nodes may be present even in patients without clinically apparent nodal disease. So, central lymph node dissection has been recommended even in case with no clinically apparent lymph node metastasis. However, the indication and the extent of prophylactic central neck dissection (pCND) have been a subject of debate for several decades.[5-8] The current guidelines recommend considering pCND in patients with advanced primary tumors (T3 or T4) or high-risk PTC.[5,9,10] However, there is insufficient clear evidence regarding this approach.

Proponents of pCND argue that PTC has a high incidence of lymph node metastasis, and therefore, the removal of micro-metastases in the central compartment lymph nodes could prevent recurrence and improve survival.[6,11] Additionally, it offers the advantage of avoiding the need for additional surgery in the future, which is associated with a higher complication rate when performed due to recurrence.[7] Furthermore, there is a growing need for a pathological report on lymph node status to accurately determine the cancer stage and make decisions regarding the necessity of postoperative radioactive iodine (RAI) therapy.[12]

However, pCND typically carries the disadvantage of potentially causing postoperative complications such as permanent hypoparathyroidism and damage to the recurrent laryngeal nerve.[6,13] Some argue that it remains unclear whether micro-metastases detected through pCND actually have a significant impact on recurrence and survival.[14,15] Additionally, there are concerns that tumor upstaging due to pCND may result in unnecessary RAI therapy.[8]

To minimize the surgical morbidity and clarify the impact of pCND on prognosis, it is crucial to address the current gap in research on the role of pCND. However, there is a little study about the role of pCND in locally advanced PTC cases. Therefore, our study aims to assess the role of pCND in clinically node-negative (cN0) T3/T4 PTC cases.

Subjects and Methods

Study population and design

We conducted a retrospective single-center study on patients with cN0 PTC who underwent total thyroidectomy (TT) with or without pCND from 1995 to 2022. All patients underwent preoperative neck ultrasound (US) or computed tomography (CT) for clinical staging before surgery. Patients who have clinically apparent metastatic lymph node, thyroid cancer other than PTC and distant metastases were excluded from the study. Additionally, patients with insufficient or missing medical records were also excluded from the analysis.

The extent of pCND is defined by the American Thyroid Association (ATA) consensus statement, with the surgical procedure determined by the operating surgeon.[16] In general, the ipsilateral pCND includes the removal of the prelaryngeal, pretracheal, and ipsilateral paratracheal lymph nodal basin.

Postoperative RAI therapy was performed 2−3 months after the operation, using 30−150 mCi in selected patients with extrathyroidal extension (ETE), cervical lymph nodes (LNs) metastasis, or high-risk pathological features.

Patients were categorized by according to the 8th AJCC staging system for thyroid cancer.[4] So, early cases who have microscopic ETE, which was previously classified as T3 in the 7th edition, was down staged and gross ETE beyond the strap muscles was classifiec as T4 according to 8th edition. Gross ETE was defined as including cases where invasion was visually confirmed during surgery, even if limited to the strap muscles. Gross ETE invading only strap muscles was classified as T3, and gross ETE into surrounding neck structures beyond strap muscle was classified as T4.

We examined demographic and clinicopathological information, including age, sex, tumor size, multifocality, lymphovascular invasion (LVI), ETE, occult LN metastasis rate, the number of metastatic LNs, RAI therapy, structural recurrence, and survival.

The patients were followed up with tests including physical examinations, neck US examinations, and stimulated or suppressed serum thyroglobulin (Tg) measurements with 6-month intervals for the first 5 years after surgery. Thereafter, they had annual follow-up examinations.

This retrospective study received approval from the Institutional Review Board of Hanyang University Guri Hospital (IRB No. 2024-07-018) and was conducted in accordance with the principles outlined in the Declaration of Helsinki.

Statistical analysis

All statistical analyses were performed using IBM SPSS statistics software (version 25.0; IBM Corp.). Categorical variables were summarized as frequencies and proportions, and differences between groups were assessed using either

the chi-square test or Fisher's exact test, as appropriate. Continuous variables were described using means±standard deviation. Group comparisons for continuous data were performed using the independent t-test or the Mann–Whitney U test, according to the distributional characteristics of the variables. Survival analysis for recurrence-free survival (RFS) was calculated using Kaplan–Meier curves. The log-rank test was used to identify differences in Kaplan–Meier survival curves. The relationship between each variable and LN metastasis was calculated using logistic regression, with odds ratios estimated along with 95% confidence intervals (CI). To determine factors independently associated with recurrence, univariate and multivariate Cox models were applied. Statistical significance was defined by a two-sided p-value <0.05.

Results

Patients' characteristics and pattern of central lymph node metastasis

A total of 1050 cN0 PTC patients were enrolled in this study. According to 8th AJCC staging system, 950 patients were classified as T1/2, and 100 patients were classified as T3/T4. The

Table 1. Clinicopathologic characteristics of patients with clinically node-negative papillary thyroid carcinoma

	T1/T2 (n=950)	T3/T4 (n=100)	p
Sex			0.787
Male	175 (18.4)	20 (20.0)	
Female	775 (81.6)	80 (80.0)	
Age (yr)	51.11±11.94	51.70±16.16	0.725
Gross ETE	0	94 (94.0)	<0.001
LVI	117 (12.3)	30 (30.0)	<0.001
Multiplicity	357 (37.6)	34 (34.0)	0.515
Bilaterality	270 (28.4)	31 (31.0)	0.642
Main tumor size (mm)	9.95±6.60	18.52±12.31	<0.001
Main tumor location			0.869
Right	335 (35.3)	31 (31.0)	
Left	307 (32.3)	34 (34.0)	
Isthmus	35 (3.7)	4 (4.0)	
Bilateral	273 (28.7)	31 (31.0)	
T category			<0.001
T1/T2/T3/T4	871 (91.7)/79 (8.3)/0/0	0/0/57 (57.0)/43 (43.0)	
N category			0.328
Nx/N0/N1a	200 (21.1)/472 (49.7)/278 (29.3)	17 (17.0)/47 (47.0)/36 (36.0)	
AJCC stage			<0.001
I/II/III/IV	878 (92.4)/72 (7.6)/0/0	52 (52.0)/30 (30.0)/18 (18.0)/0	
pCND			0.367
Non-pCND	200 (21.1)	17 (17.0)	
pCND	750 (78.9)	83 (83.0)	
Ipsilateral	442 (46.5)	49 (49.0)	>0.999
Bilateral	308 (32.4)	34 (34.0)	
LN metastasis*	278/750 (37.1)	36/83 (43.4)	0.283
Ipsilateral*	162/750 (21.6)	18/83 (21.7)	>0.999
Bilateral*	12/308 (3.9)	1/34 (2.9)	>0.999
Number of harvested LNs	7.58±5.68	7.17±6.20	0.538
Number of metastatic LNs	1.06±2.14	1.52±2.85	0.157
RAI therapy	643 (67.7)	83 (83.0)	0.002
Mean administered activity of RAI (mCi)	105.62±59.37	122.13±43.70	0.015
Follow-up period (month)	85.68±68.30	99.35±65.96	0.056
Recurrence	8 (0.8)	5 (5.0)	0.005

Data are presented as mean±standard deviation or n (%). *proportion calculated only for patients who underwent bilateral pCND. ETE, extrathyroidal extension; LVI, lymphovascular invasion; AJCC, American Joint Committee on Cancer; pCND, prophylactic central neck dissection; LN, lymph node; RAI, radioactive iodine.

clinicopathological, and tumor characteristics of both groups are presented in Table 1. Between the two groups, there were no significant differences in age, sex, multiplicity, bilaterality, N category, the extent of CND and follow-up period. However, T3/T4 group showed statistically significant higher in the prevalence of gross ETE, LVI, postoperative RAI therapy, mean administered activity of RAI and recurrence. There were 4 deaths (0.4%) in the T1/T2 group and 1 death (1.0%) in the T3/T4 group, but there were no deaths due to thyroid cancer.

In the T1/T2 group, 200 patients did not undergo CND, while 750 patients underwent CND, including 308 bilateral pCND. In the T3/T4 group, 17 patients did not undergo pCND, while 83 patients underwent pCND including 34 bilateral pCND. When comparing the two groups among the 833 patients who underwent pCND, occult central lymph node metastasis (CLNM) was not significantly different (37.1% in the T1/T2 group vs. 43.4% in the T3/T4 group, p=0.283). When examining the rate of bilateral LN metastasis in patients who underwent bilateral pCND with the tumor confined to one side, bilateral central compartment metastasis rate was also not different 3.9% in the T1/T2 group vs. 2.9% in the T3/T4 group, p>0.999). The average number of removed LNs and metastatic LNs showed no significant difference between the two groups (p=0.538 and p=0.157, respectively). There were 8 (0.8%) in the T1/T2 group and 5 (5.0%) in the T3/T4 group of recurrence during mean follow up of 85.7 months and 99.3 months, respectively.

Risk factors of CLNM and risk of recurrence in cN0 T1-T4 PTC

Table 2 shows factors related to CLNM in cN0 T1-T4 PTC. In multivariate analysis, only younger age (<55), male gender, LVI, and tumor size (>20 mm) were significantly correlated with CLNM (p<0.001, p=0.014, p<0.001, and p=0.001, respectively).

Using Cox proportional hazards regression model for all cN0 PTC patients, LVI, T3/T4 categories, Gross ETE, and CLNM were significantly associated with recurrence in univariate analysis (Table 3). However, in multivariate analysis, only gross ETE and CLNM was associated with recurrence

Table 2. Logistic regression analysis of related factors of central lymph node metastasis in clinically node-negative T1–T4 PTC patients

Factors	Univariate		Multivariate	
	OR (95% CI)	p	OR (95% CI)	p
Age (≥55 years)				
<55	-		-	
≥55	0.425 (0.315–0.575)	<0.001	0.422 (0.305–0.585)	<0.001
Sex				
Female	-		-	
Male	1.876 (1.325–2.565)	<0.001	1.610 (1.103–2.349)	0.014
LVI				
No	-		-	
Yes	6.932 (4.486–10.713)	<0.001	6.018 (3.829–9.457)	<0.001
Multiplicity				
No	-		-	
Yes	1.423 (1.070–1.893)	0.015	1.239 (0.730–2.101)	0.427
Bilaterality				
No	-		-	
Yes	1.379 (1.019–1.865)	0.037	1.057 (0.603–1.851)	0.846
Tumor size				
≤20 mm	-		-	
>20 mm	2.499 (1.609–3.881)	<0.001	2.265 (1.398–3.670)	0.001
T category				
T1/T2	-			
T3/T4	1.300 (0.822–2.057)	0.262		
Gross ETE				
No	-			
Yes	1.311 (0.818–2.100)	0.260		

PTC, papillary thyroid carcinoma; OR, odds ratio; CI, confidence interval; LVI, lymphovascular invasion; ETE, extrathyroidal extension.

Table 3. Cox regression analysis for risk of recurrence in clinically node-negative T1–T4 PTC patients

Factors	Univariate		Multivariate	
	HR (95% CI)	*p*	HR (95% CI)	*p*
Age (≥55 years)	0.487 (0.134–1.774)	0.275		
Sex, male	3.021 (0.987–9.249)	0.053		
LVI	3.390 (1.037–11.075)	0.043	1.708 (0.468–6.225)	0.418
Multiplicity	1.929 (0.645–5.772)	0.240		
Bilaterality	2.899 (0.971–8.655)	0.057		
Tumor size (>20 mm)	2.461 (0.675–8.971)	0.172		
T3/T4	5.028 (1.619–15.620)	0.005		
Gross ETE	5.249 (1.687–16.331)	0.004	4.332 (1.353–13.872)	0.014
RAI therapy	1.228 (0.270–5.579)	0.790		
CLNM	3.941 (1.289–12.051)	0.016	3.265 (1.006–10.592)	0.049
pCND	0.676 (0.205–2.224)	0.519		

PTC, papillary thyroid carcinoma; HR, hazard ratio; CI, confidence interval; LVI, lymphovascular invasion; ETE, extrathyroidal extension; RAI, radioactive iodine; CLNM, central lymph node metastasis; pCND, prophylactic central neck dissection.

(p=0.014, p=0.049, respectively).

Surgical outcomes and risk of recurrence in cN0 T3/T4 PTC

The surgical outcomes, postoperative RAI and the pattern of recurrence in cN0 T3/T4 group are listed according to the pCND in Table 4. Postoperative RAI therapy was performed more in the pCND group compared to the non-pCND group (59.8% vs. 88.0%, p=0.008). However, there were no significant differences in RAI dose and stimulated Tg between two groups (p=0.196, p=0.492, respectively). Regarding the size of the metastatic deposits, the pathological records for the size of occult CLNM were available for 12 out of 36 patients in the T3/T4 pCND group. Among these, all three patients in the pCND group who experienced recurrence were identified as having macrometastases (>2 mm).

In the comparison of postoperative complications, preoperative vocal fold palsy was observed in one case in the non-pCND group and five cases in the pCND group. After excluding cases with preoperative vocal fold palsy, no statistically significant differences were observed in both transient and permanent vocal fold palsy. Although there were no statistical difference in the other postoperative complications between the two groups, transient hypoparathyroidism was significantly higher in the pCND group (p=0.015).

The specific patterns of recurrence in the cN0 T3/T4 group were further analyzed. All five recurrence cases involved the lateral LNs (level II, III, or IV), while no central LN recurrences were observed in either group. In the pCND group, one of the four recurrent cases had suspected recurrence at both the operative bed and a lateral LN on US; this case was duplicated in the site-specific analysis. Specifically, lateral neck recurrences were identified at right levels III and IV (two cases), left levels II and III (one case), and right level III (two cases). Furthermore, there were no cases of distant metastasis or death due to thyroid cancer. The 5-year RFS rate was not significantly different between the two groups (100% in the non-pCND group vs. 95.5% in the pCND group, p=0.754) (Fig. 1).

In cN0 T3/T4 PTC patients, univariate Cox proportional hazards regression analysis identified male gender as the only variable reaching statistical significance; however, no other clinicopathologic factors were significantly associated with recurrence (Table 5).

Discussion

The controversies regarding pCND has been persisted for several decades. Over the years, a transition from an era advocating aggressive pCND to the current practice of narrowing indication and extent of surgery, although it is clear that CLNM has a negative impact on prognosis with decreased. CLNM in differentiated thyroid cancer (DTC) patients is a significant risk factor for lateral LN metastasis and has been shown to increase the risk of recurrence[17-19] and associated with decreased overall survival (OS).[20]

Consequently, for cN1 PTC patients, therapeutic CND is widely accepted as the standard treatment in conjunction with thyroidectomy. However, the management of central LNs in cN0 PTC patients remains a subject of ongoing debate.

Several studies have demonstrated pCND may lead to reduced recurrence and mortality rates,[6] improved staging ac-

curacy (e.g., converting Nx to N1a, upstaging patients over 55 years of age from AJCC stage I to stage II),[6,11] lower Tg levels,[21] enhanced suitability for RAI treatment,[22] and a reduced need for reoperative surgery.[11,13] So, some authors have advocated pCND given the importance of achieving complete surgical resection to improve recurrence and survival outcomes, while there is a lack of randomized controlled data to confirm the impact of routine pCND on recurrence or survival rates in DTC.

Postoperative Tg is a well-established marker for monitoring residual or recurrent disease in DTC patients. The Tg level at the time of RAI administration serves as an early prognostic indicator,[23] and several studies have shown that TT with pCND results in lower postoperative preablative Tg levels compared to TT alone,[21] guiding both risk stratification and patient selection for RAI therapy.[22] Supporters of pCND note that postoperative complications are not significantly

Table 4. Surgical outcomes of clinically node-negative T3/T4 PTC according to pCND

T3/T4	Non-pCND (n=17)	pCND (n=83)	*p*
RAI therapy	10 (59.8)	73 (88.0)	0.008
RAI activity (mCi)	98.89±55.55	125±41.58	0.196
Stimulated Tg (ng/mL)	5.68±9.17	10.09±27.79	0.492
Complications			
Transient RLN palsy	3 (18.8)	11 (13.3)	0.702
Permanent RLN palsy*	0	6 (7.2)	0.586
Transient hypoparathyroidism	3 (17.6)	43 (51.8)	0.015
Permanent hypoparathyroidism	2 (11.8)	5 (6.0)	0.340
Hematoma	0	0	>0.999
Seroma	4 (23.5)	16 (19.3)	0.741
Number of harvested LNs	0	7.17±6.20	
Number of metastatic LNs	0	1.52±2.85	
Macrometastases	0	7/12†	0.599
Recurrence	1 (5.9)	4 (4.8)	>0.999
Site of recurrence			
Thyroid bed	0	1‡	
Central LN	0	0	
Lateral LN	1	4‡	
Distant	0	0	
T3	**Non-pCND (n=11)**	**pCND (n=46)**	***p***
Recurrence	1 (9.1)	2 (4.3)	>0.999
Site of recurrence			
Thyroid bed	0	0	
Central LN	0	0	
Lateral LN	1	2	
Distant	0	0	
T4	**Non-pCND (n=6)**	**pCND (n=37)**	***p***
Recurrence	0	2 (5.4)	0.092
Site of recurrence			
Thyroid bed	0	1‡	
Central LN	0	0	
Lateral LN	0	2‡	
Distant	0	0	

Data are presented as mean±standard deviation or n (%). *cases with preoperative stage vocal fold palsy were excluded; †pathological records for the size of metastatic lymph nodes were available for only 12 out of 36 patients with occult central lymph node metastasis; ‡a case with suspected recurrence at both OP bed and lateral lymph node on US was duplicated. PTC, papillary thyroid carcinoma; pCND, prophylactic central neck dissection; RAI, radioactive iodine; RLN, recurrent laryngeal nerve; LN, lymph node; Tg, thyroglobulin.

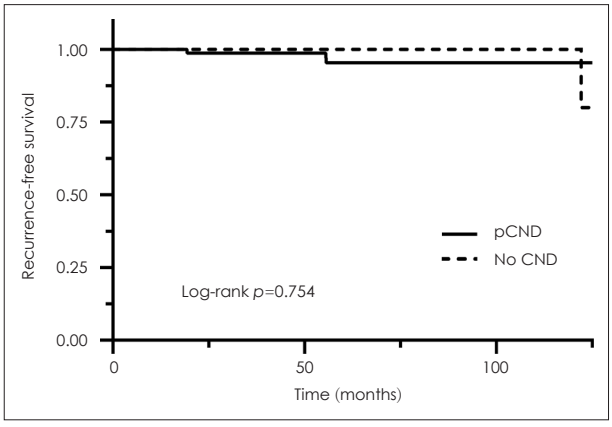

Fig. 1. Kaplan–Meier curves for recurrence-free survival of clinically node-negative T3/T4 PTC patients. PTC, papillary thyroid carcinoma; pCND, prophylactic central neck dissection.

Table 5. Cox regression analysis for risk of recurrence in clinically node-negative T3/T4 PTC

Factors	Univariate	
	HR (95% CI)	*p*
Age (≥55 years)	0.746 (0.124–4.488)	0.749
Sex, male	7.590 (1.193–48.279)	0.032
LVI	9.226 (0.946–89.944)	0.056
Multiplicity	0.672 (0.072–6.306)	0.728
Bilaterality	0.745 (0.080–6.954)	0.796
Tumor size (>20 mm)	1.604 (0.268–9.609)	0.605
T category (T4)	0.843 (0.139–5.101)	0.852
Gross ETE	N/A*	
RAI therapy	0.415 (0.046–3.778)	0.435
CLNM	3.292 (0.539–20.122)	0.197
pCND	0.705 (0.079–6.326)	0.755

*all recurrence was observed in PTC with gross ETE. PTC, papillary thyroid carcinoma; HR, hazard ratio; CI, confidence interval; LVI, lymphovascular invasion; ETE, extrathyroidal extension; RAI, radioactive iodine; CLNM, central lymph node metastasis; pCND, prophylactic central neck dissection.

increased, as confirmed by a recent systematic review of randomized controlled trials reporting similar complication rates in cN0 PTC patients treated with TT±pCND[15]; complications are often attributable to thyroidectomy itself, and recurrent laryngeal nerve dysfunction is usually temporary. Importantly, recurrence risk correlates with the number of metastatic LNs at initial presentation,[19,24,25] with five or more CLNMs (<2 mm) or macrometastases (>2 mm) associated with higher recurrence,[3] a finding incorporated into the 2025 ATA risk stratification. Despite advances in high-resolution US and CT, preoperative evaluation of the central compartment remains unreliable,[26,27] making appropriate risk assessment for CLNM difficult without pCND.

Wada, et al.[28] conducted a retrospective study comparing disease-free survival (DFS) and disease-specific survival between 42 patients who underwent therapeutic central neck dissection for clinically evident LN metastases and 92 patients who underwent prophylactic dissection. They found that microscopic CLNM were not significantly associated with recurrence or survival, whereas macroscopic metastases were significantly correlated with poorer RFS.[28] Moreno, et al.[29] retrospectively analyzed 135 patients with PTC who underwent TT with or without central neck dissection. They found that preoperative central neck US detected only macroscopic nodal disease, and that patients with negative central neck US findings had excellent long-term regional control and OS, regardless of the presence of microscopic metastases on pathology or the patient's age. In contrast, macroscopic nodal metastases identified preoperatively were significant predictors of recurrence and disease-specific survival, indicating that pCND did not significantly impact long-term outcomes in patients without clinically evident nodal disease. Consistent with these findings, Randolph, et al.,[3] in a review of the literature, concluded that the prognostic impact of nodal metastases is largely determined by the size and number of metastatic LNs and the presence of extranodal extension, with micrometastases (<2 mm) having limited influence on recurrence, while macrometastases (>2 mm) and extranodal extension are associated with higher recurrence risk and poorer outcomes.

Systematic reviews show conflicting result on the impact of pCND; some studies indicate the pCND does not influence recurrence,[14,15] while others suggest it may reduce the risk of recurrence.[30,31] However, the extent to which pCND reduces the risk of recurrence may be related to the increased use of RAI ablation, making its precise impact still unclear. There is little evidence to suggest that pCND improves OS in cN0 PTC. In terms of recurrence, DFS and RFS, several retrospective studies have found no significant difference between patients undergoing TT with or without pCND.[32-34] Costa, et al.[32] retrospectively analyzed 244 cN0 PTC patients and found no significant difference in DFS between patients who underwent TT with pCND and those who had TT alone. Similarly, Zuniga and Sanabria[33] reviewed 266 cN0 PTC patients and reported that prophylactic dissection did not significantly alter recurrence rates during long-term follow-up. More recently, Yoo, et al.[34] analyzed a total of 477 cN0 PTC patients and applied propensity score matching to create two well-balanced groups of 135 patients each, observing no significant difference in RFS between the pCND and non-pCND groups. This is further supported by the prospective randomized controlled trial of 181 patients, which demonstrated that pCND did not significantly affect recurrence or long-term outcomes compared with TT alone.[35]

While pCND may enhance the accuracy of staging, it can lead to upstaging, resulting in more patients undergoing RAI therapy and receiving higher doses of RAI.[36] Especially for T3 and T4 PTC, which are already considered candidates for RAI in several guidelines, the significance of precise staging in locally advanced PTC might be limited. Moreover, it's conceivable that many cases of micro-metastasis could be effectively managed by RAI treatment. In our study, RAI therapy was more frequently administered in the pCND group compared to the non-pCND group. This discrepancy likely reflects the upstaging effect (pN0 to pN1a) achieved through the pathologic identification of occult metastases by pCND. While it is possible that more frequent RAI administration could have influenced the favorable outcomes in the pCND group, it is noteworthy that the non-pCND group also demonstrated excellent regional control despite receiving RAI therapy less frequently. These observations may suggest that, in the context of cN0 T3/T4 PTC, current baseline management strategies might provide sufficient regional control even without the routine implementation of pCND. Consequently, the incremental benefit of performing pCND to identify occult metastases and potentially escalate RAI therapy might be relatively modest in this specific clinical setting.

Additionally, there are several studies that present opposing results to the notion that pCND lowers postoperative Tg levels. In a retrospective study, pCND did not impact the postablative sTg levels or the number of athyroglobulinemia cases.[36] In the study by Lang, et al.,[21] preablative sTg levels and

the presence of athyroglobulinemia were observed to be higher in the pCND group, but these differences lost statistical significance 6 months after surgery. These findings suggest that adding pCND may have little impact on the microscopic residual disease burden.

Over time, the role of pCND has been re-estimated, as reflected in several guidelines, which no longer recommend pCND for low-risk PTC. According to the 2009 ATA guidelines, pCND could be performed in patients with papillary carcinoma. However, the updated 2025 ATA guidelines specify that pCND should exclusively be contemplated for cases who have cNo patients with advanced primary tumors (T3 or T4), or if the information will be used to plan further treatment.[5] This recommendation is graded as conditional and supported by low-certainty evidence.

The majority of participants in past studies focused on T1/T2, and due to changes in AJCC staging system, many patients who were previously classified as pT3 have now been reclassified as pT1/T2. This transition has resulted in limited research on advanced PTC. We used the T category according to the 8th AJCC staging system to investigate the role of pCND in T3/T4 PTC.

In cN0 T3/T4 PTC, the occult metastasis rate was not statistically different from T1/T2 group, although it is slightly higher (37.1% in T1/T2 and 43.4% in T3/T4 PTC). Recurrence rates and 5-year RFS according to the pCND were also not significantly different between the two groups. Additionally, our study found no significant differences in stimulated-Tg levels, which are used as markers for predicting recurrence or persistent disease.

To better understand these findings, we evaluated the size of the metastatic deposits. Although our study was limited by the retrospective availability of LN size data for all cases, the findings from the available subset align with recent consensus: all confirmed recurrences in the pCND group occurred in patients with macrometastases (>2 mm). This observation suggests that while pCND may identify occult metastases, its impact on reducing recurrence might be clinically negligible for patients with only micrometastases.

Another striking finding in our study was that all regional recurrences occurred exclusively in the lateral neck compartment, with no central compartment recurrences observed even in the non-pCND group. The absence of central recurrence in patients who did not undergo formal pCND can be attributed to several factors. First, postoperative RAI therapy, which was administered to a substantial portion (59.8%) of the non-pCND group, may have effectively eradicated any occult microscopic residual disease in the central basin.[5,23] Second, the biological behavior of some locally advanced PTCs may favor "skip metastases," where tumor cells drain directly into the lateral neck nodes, bypassing the central compartment entirely.[37,38] Lastly, a meticulous TT inherently involves the incidental removal of pericapsular soft tissue and microscopic lymphatic networks. Even if distinct LNs are not pathologically identified or harvested, the clearance of this adjacent tissue may provide sufficient local disease control in true cN0 patients. Consequently, our findings suggest that for cN0 T3/T4 PTC patients, diligent preoperative and postoperative surveillance of the lateral neck may yield greater clinical benefit than performing routine prophylactic central clearance.

Therefore, the benefits of recommending pCND in T3/T4 PTC in several guidelines are questionable. Based on the results of our study, pCND may have little effect on recurrence even in T3/T4 PTC with increased hypoparathyroidism as a complication. So, pCND may not be routinely performed in T3/T4 PTC.

There were some limitations to this study. Firstly, the limited number of patients who underwent bilateral pCND hinders an accurate evaluation of the occult contralateral CLNM rate and the recurrence rates according to pCND. Secondly, RAI therapy was significantly more common in the group that underwent pCND, which could confound the evaluation of recurrence rates by potentially influencing outcomes. Furthermore, although T3 and T4 tumors may have different prognostic characteristics, we had to combine them for the survival analysis because the extremely low number of recurrence events in each separate subgroup limited the statistical power of the models.

Nevertheless, to our knowledge, our study is the largest single-center cohort study utilizing the AJCC 8th Edition staging system focused on the role of pCND in cN0 T3/T4 PTC. Notably, by excluding microscopic ETE from the T3 category in accordance with this modern staging context, our research provides a more precise evaluation of true locally advanced disease compared to previous studies. Further investigation through large-scale prospective research will be important to confirm our findings and provide more robust evidence regarding the necessity of pCND in T3/T4 PTC.

In conclusion, occult metastasis rate was not different between the T3/T4 group than T1/T2 group in PTC. There were also no significant differences in recurrence rate and 5-year RFS according to pCND in cN0 T3/T4 PTC cases. Further-

more, there was no recurrence in the central LN and all of recurrence occurred at the lateral lymph compartment. So, the impact of pCND on recurrence in T3/T4 PTC patients might be limited with increased complication. Routine pCND might be unnecessary even in cN0 T3/T4 PTC.

Author Contribution

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