

Is Central Lymph Node Dissection Mandatory in 2 cm or Less Sized Papillary Thyroid Cancer?

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Purpose: There have been controversies on the scope of central lymph node dissection (CND) in papillary thyroid cancer (PTC). We performed this study to determine the role of CND for patients having PTC measuring 2 cm or less.

Methods: 530 cases of PTC less than 2 cm had undergone lobectomy plus isthmectomy (LI) with CND or without CND. Clinicopathologic records and clinical outcome were evaluated, retrospectively.

Results: Comparing recurrence rates in LI with CND group (4/174, 2.30%) and LI without CND group (16/356, 4.49%), there was no significant statistical difference in recurrence ($P=0.331$). We compared 20 patients with recurrences and 510 patients of no recurrence. The size of tumor seemed to influence recurrence ($P<0.001$) and the size of tumor developing recurrence was larger than the other (1.11 cm vs. 0.75 cm). When considering division into PTC and papillary thyroid microcarcinoma (PTMC), PTMC showed less recurrence significantly ($P=0.006$). No other variables such as age, sex, tumor location, extrathyroidal extension seemed to be related to the recurrence.

Conclusion: We could not find any relevant role of CND to prevent recurrence either locally or regionally in cases of no lymph node metastasis after CND for patients having PTC measuring 2 cm or less. Moreover, prophylactic CND is not mandatory for all cases of PTC less than 2 cm. (*J Korean Surg Soc* 2010;79:332-339)

Key Words: Papillary thyroid cancer, Central lymph node dissection, Recurrence, Prophylactic lymph node dissection

INTRODUCTION

As papillary thyroid cancer (PTC) is the most prevalent histologic type of differentiated thyroid cancer, it comprises 95.6% of differentiated thyroid cancer in Korea.⁽¹⁾ Mostly, treatment of PTC means thyroidectomy, thyroxine medication suppressing thyroid-stimulating hormone, and radioactive iodine ablation following total thyroidectomy. According to the recent treatment guidelines by American Thyroid Association (ATA) in 2009, total thyroidectomy was recommended in case of PTC measuring 1 cm or

more, and lobectomy could be implemented for unilateral papillary thyroid microcarcinoma (PTMC) confined within thyroid having low risk factors.⁽²⁾

On the contrary, lobectomy can be considered even in case of PTC measuring 4 cm or less and classified as low risk patient by the guidelines from current National Comprehensive Cancer Network (NCCN).⁽³⁾

Although some said adjacent cervical lymph nodes may harbor cancer cells in about 30~90% of PTC,^(4,5) there have been controversies on the scope of regional lymph node dissection by now. We can notice some changes on the recommendation of central lymph node dissection (CND) in the guidelines by ATA. In 2006, ATA recommended routine CND for PTC,⁽⁶⁾ but they changed their stance back to possible prophylactic CND for locally advanced T3 or T4 PTC in 2009.⁽²⁾

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Due to the controversial issues on the CND, we tried to determine the role of CND for patients having PTC measuring 2 cm or less.

METHODS

Between February 1982 and November 2009, 1,321 cases of thyroidectomies had been performed for primary thyroid cancer at the division of thyroid surgery. Among them, 577 cases were selected according to the selection criteria: all patients having PTC less than 2 cm-sized index tumor with NO or NX of lymph node status, who were underwent lobectomy with isthmectomy (LI). Approval of institutional review board for this retrospective study was gained right before the retrieving patients' list from the hospital data base. Forty-seven cases were ineligible in this study due to follow-up loss immediately after first postoperative ambulatory care. Therefore forty-seven cases were excluded from the study population and remaining 530 patients were included in this study finally.

As expected, we could locate results of ultrasonographic findings with or without cytologic aspiration following positive radiologic suggestions in all cases. LI was performed in cases of unilateral thyroid tumor (less than 2 cm in maximum diameter) suggesting malignancy in fine-needle aspiration cytology (FNAC), no suspicious nodule in the contralateral lobe. We performed unilateral CND only in cases of having suspicious central lymph nodes by ultrasonography with or without FNAC, or suspicious central lymph node detected incidentally during the operation. Therapeutic CND was carried out to harvest pretracheal, paratracheal and Delphian lymph nodes, while thyroid gland being dissected away. Therefore, we included 356 patients underwent LI without CND and 174 patients underwent LI with CND and confirmed being without central lymph node metastasis after CND in this study.

Follow-up studies comprises of routine cervical ultrasonography, thyroid function test and computerized tomogram, if needed. At postoperative six months and 1 year after, cervical ultrasonography and thyroid function test were performed. After that, semiannual thyroid function

test and annual cervical ultrasonography were carried out on a regular basis. Additional FNAC should be done to verify any possible recurrence or metastasis at the operative thyroid bed or cervical lymph nodes after ultrasonography.

Transient hypocalcemia was defined as complete recovery from the symptomatic and biochemical hypocalcemia

Table 1. Clinicopathologic characteristics of 530 papillary thyroid carcinoma patients underwent lobectomy with isthmectomy

Variables	Results
Age, mean (range), yr	45.6 (15~76)
Sex	
Male	64 (12.08%)
Female	466 (87.92%)
Tumor size, mean (range), cm	0.77 (0.05~2.00)
≤ 1 cm	430 (81.13%)
≤ 2 cm, 1 cm <	100 (18.87%)
Tumor location	
Upper	100 (18.39%)
Mid	306 (57.37%)
Lower	95 (17.92%)
Isthmic	29 (5.47%)
T stage	
T1	447 (84.34%)
T3	83 (15.66%)
Distant metastasis	
Absent	530 (100.00%)
Present	0 (0.00%)
Encapsulation	
Absent	446 (84.15%)
Focally present	35 (6.60%)
Present	49 (9.25%)
Necrosis	
Absent	529 (99.81%)
Present	1 (0.19%)
Capsular invasion	
Absent	281 (53.02%)
Present	249 (46.98%)
Extrathyroidal extension	
Absent	447 (84.34%)
Present	83 (15.66%)
Lymphatic invasion	
Absent	525 (99.06%)
Present	5 (0.94%)
Vascular invasion	
Absent	526 (99.25%)
Present	4 (0.75%)
Recurrence	
Absent	510 (96.23%)
Present	20 (3.77%)
Duration of follow up, mean (range), mo	27.37 (1~253)

without medical aid within six months after initial operation. Permanent hypocalcemia means failure of recovery from the hypocalcemia more than six months from the thyroidectomy. Transient vocal cord paralysis means satisfiable regain of vocal quality within a year after thyroidectomy. Permanent vocal cord paralysis was the case of complete and irreversible loss of preoperative voice.

We retrospectively evaluated patients' medical records,

pathologic reports, and operation records as well as radiologic findings suggesting possible lymph node metastasis.

For statistical verification, chi-square test, Fisher's exact test, and independent t-test were done to determine relation between CND and PTC less than 2 cm in maximum diameter. Kaplan-Meier survival analysis was performed by the log-rank test. P-value less than 0.05 was

Table 2. Comparison of clinicopathologic variables of 530 papillary thyroid carcinoma patients between LI with unilateral CND and LI only

Variables	LI* with CND [†] (n=174)	LI without CND (n=356)	P-value
Age, mean (SD [‡]), yr	45.39 (±10.82)	45.72 (±10.19)	0.728
Sex			
Male	17 (9.77%)	47 (13.20%)	0.320
Female	157 (90.23%)	309 (86.80%)	
Tumor size, mean (SD), cm	0.7221 (±0.37)	0.7904 (±0.45)	0.085
Tumor location			
Upper	34 (19.54%)	66 (18.54%)	0.738
Mid	97 (55.75%)	209 (58.71%)	
Lower	35 (20.11%)	60 (16.85%)	
Isthmic	8 (4.60%)	21 (5.90%)	
T stage			
T1	140 (80.46%)	307 (86.24%)	0.098
T3	34 (19.54%)	49 (13.76%)	
Encapsulation			
Absent	147 (84.48%)	299 (83.99%)	1.000
Focally present	11 (6.32%)	24 (6.74%)	
Present	16 (9.20%)	33 (9.27%)	
Necrosis			
Absent	174 (100.00%)	355 (99.72%)	1.000
Present	0 (0.00%)	1 (0.28%)	
Capsular invasion			
Absent	85 (48.85%)	196 (55.06%)	0.195
Present	89 (51.15%)	160 (44.94%)	
Extrathyroidal extension			
Absent	140 (80.46%)	307 (86.24%)	0.098
Present	34 (19.54%)	49 (13.76%)	
Lymphatic invasion			
Absent	172 (98.85%)	353 (99.16%)	0.665
Present	2 (1.15%)	3 (0.84%)	
Vascular invasion			
Absent	174 (100.00%)	352 (98.88%)	0.308
Present	0 (0.00%)	4 (1.12%)	
Recurrence			
Absent	170 (97.70%)	340 (95.51%)	0.331
Present	4 (2.30%)	16 (4.49%)	
Duration till recurrence, mean (range), mo	33.00 (8~97)	44.94 (9~246)	0.704
Duration of follow up, mean (range), mo	20.21 (1~111)	30.87 (1~253)	<0.001

*LI = lobectomy plus isthmectomy; [†]CND = central lymph node dissection; [‡]SD = standard deviation.

considered as significant.

RESULTS

Mean age of patients was 45.6 years, and mean follow-up period was 27.37 months. Female patients were 466 and male were 64, mean diameter of index thyroid cancer was 0.77 cm. Capsular invasion was located in 249 cases (46.98%) and extrathyroidal extension was reported in 83 cases (15.66%) (Table 1). According to the TNM classification, all patients were categorized into either T1/T3N0M0 or T1/T3NxM0. Twenty patients (3.77%, 20/530) yielded recurrences which developed 42.55 months after operation in average. The number of harvested central lymph nodes was 473, so 2.72 lymph nodes were retrieved after therapeutic CND in average (range: 1~12).

Comparing LI with unilateral CND (174 cases) and LI only (356 cases), there was no significant clinicopathologic differences (Table 2). Having 4 cases of recurrences in the former group (LI+CND) and 16 cases in the latter (LI only), we failed to show statistical significance, which meant no meaningful oncologic outcome could be seen between performance of CND or not (P=0.331).

As postoperative complication, we compared the incidence of hoarseness (Table 3). We found 4 transient hoarseness in LI+CND group and 5 in LI only group that meant no differences in developing postoperative transient

hoarseness (P=0.485). Thirty-seven parathyroid glands were incidentally sacrificed *in toto*, therefore 0.07 parathyroid gland meant to be took away per case. When it happened, one parathyroid gland was really removed incidentally during the operation per patient. The incidence of postoperative transient hypocalcemia was not different statistically (P=0.698).

We compared 20 patients with recurrences and 510 patients of no recurrence (Table 4). The size of index tumor seemed to influence recurrence (P<0.001), and we found the size of tumor developing recurrence was larger than the other (1.11 cm vs. 0.75 cm). By comparing PTC and PTMC, PTMC showed less recurrence significantly (P=0.006). No other variables such as age, sex, tumor location, extrathyroidal extension seemed to be related to the recurrence.

Among the study population, PTMC were 430 cases and PTC were 100 cases. Comparing 149 cases of LI+CND and 281 cases of LI only in PTMC, we failed to prove significant differences in recurrence in spite of 4 cases of recurrence (2.68%, 4/149) and 7 recurrences (2.49%, 7/281) respectively (P=1.000). After comparison of remains except PTMC, no recurrence (0.00%, 0/25) was found in LI+CND group and 9 recurrences (12.00%, 9/75) in LI only group. There was no significant difference statistically (P=0.107). None of the variables were found to be significantly related to the recurrence in either PTC or PTMC groups.

When dividing the study population into two groups, PTMC and PTC, there was no significant changes on disease-free survival evaluated by Kaplan-Meier method (Log-rank test, =0.234) (Fig. 1).

We tabulated 20 recurrent patients in Table 5. As previously described, recurrent cases were reported 42.55 months after operation in average (range: 8~246 months). Recurrent sites were contralateral thyroid gland (15 cases), ipsilateral lateral cervical lymph node (6 cases), and one ipsilateral central lymph node. There were 2 cases of concomitant ipsilateral lateral cervical lymph node recurrence along with contralateral thyroid gland tumor formation, and one of contralateral lateral cervical lymph

Table 3. Comparison of postoperative complications of 530 papillary thyroid carcinoma patients between LI with unilateral CND and LI only

	LI* with CND [†] (n=174)	LI without CND (n=356)	P-value
Hypocalcemia			
Absent	173 (99.43%)	354 (99.44%)	0.698
Transient	1 (0.57%)	2 (0.56%)	
Permanent	0 (0.00%)	0 (0.00%)	
Vocal cord paralysis			
Absent	170 (97.70%)	351 (98.60%)	0.485
Transient	4 (2.30%)	5 (1.40%)	
Permanent	0 (0.00%)	0 (0.00%)	

*LI = lobectomy plus isthmectomy; [†]CND = central lymph node dissection.

Table 4. Comparison of clinicopathologic variables of 530 papillary thyroid carcinoma patients between recurred patients and non-recurred patients

Variables	Recurrence (+) (n=20)	Recurrence (-) (n=510)	P-value
Age, mean (SD*), yr	44.70 (\pm 11.93)	45.65 (\pm 10.34)	0.690
Sex			
Male	1 (5.00%)	63 (12.35%)	0.493
Female	19 (95.00%)	447 (87.65%)	
Tumor size, mean (SD), cm	1.11 (\pm 0.51)	0.75 (\pm 0.42)	<0.001
PTMC [†]			
Yes	11 (55.00%)	419 (82.16%)	0.006
No	9 (45.00%)	91 (17.84%)	
Tumor location			
Upper	8 (40.00%)	92 (18.04%)	0.137
Mid	9 (45.00%)	280 (54.90%)	
Lower	2 (10.00%)	93 (18.24%)	
Isthmic	1 (5.00%)	28 (5.49%)	
T stage			
T1	17 (85.00%)	430 (84.31%)	1.000
T3	3 (15.00%)	80 (15.69%)	
Encapsulation			
Absent	18 (90.00%)	428 (83.92%)	0.713
Focally present	0 (0.00%)	35 (6.86%)	
Present	2 (10.00%)	47 (9.22%)	
Necrosis			
Absent	20 (100.00%)	509 (99.80%)	1.000
Present	0 (0.00%)	1 (0.20%)	
Capsular invasion			
Absent	11 (55.00%)	270 (52.94%)	1.000
Present	9 (45.00%)	240 (47.06%)	
Extrathyroidal extension			
Absent	17 (85.00%)	430 (84.31%)	1.000
Present	3 (15.00%)	80 (15.69%)	
Lymphatic invasion			
Absent	20 (100.00%)	505 (99.02%)	1.000
Present	0 (0.00%)	5 (0.98%)	
Vascular invasion			
Absent	20 (100.00%)	506 (99.22%)	1.000
Present	0 (0.00%)	4 (0.78%)	
CND [‡]			
No	16 (80.00%)	340 (66.67%)	0.331
Yes	4 (20.00%)	170 (33.33%)	
Duration of follow up, mean (range), mo	66.45 (13~253)	25.84 (1~140)	<0.001

*SD = standard deviation; [†]PTMC = papillary thyroid microcarcinoma; [‡]CND = central lymph node dissection.

node metastasis with contralateral thyroid gland cancer. In each case of recurrences, completion thyroidectomy along with bilateral CND was followed, and additional ipsilateral or contralateral modified radical neck dissection was added in case of lateral cervical lymph node metastasis respectively. Radioactive iodine ablation was routinely performed in every case of recurrences postoperatively. We had three

unusual cases in Table 5. Number 1 reported recurrence in central lymph node, despite of CND during the initial operation for 0.8 cm-sized cancer in 50-year-old female. She had left sided PTMC without central lymph node metastasis by pathology at that time. After completion thyroidectomy with bilateral CND, pathology confirmed bilateral central lymph node metastasis. In number 15,

skull and first cervical spine metastases without symptom were accidentally reported 18 months postoperatively by incidental MRI. He had had LI only for ipsilateral PTMC

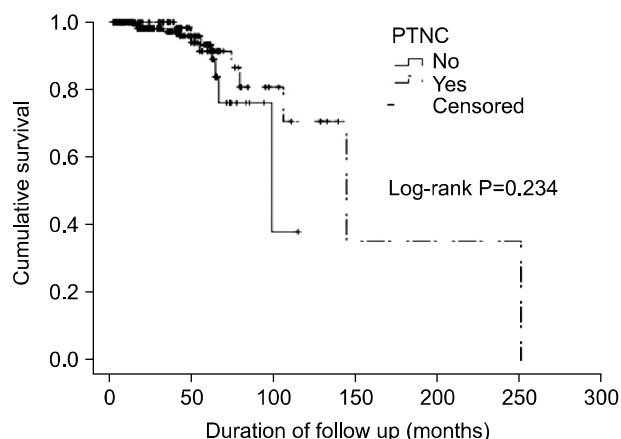


Fig. 1. Kaplan-Meier survival curve plotted by whether papillary thyroid microcarcinoma present or not.

(0.5 cm). Completion thyroidectomy was followed to implement radioactive iodine therapy after getting pathology report of contralateral PTMC (0.4 cm) without any central lymph node metastasis. In number 16, recurrences resided in contralateral thyroid gland (PTMC, 0.1 cm) and cervical lymph node (level 2 and 4). Two years ago, she had found to have left PTC measured 1.3 cm and refused to undergo CND.

In this study population, we had 83 patients of T3 (15.66%) category and their average tumor diameter was 0.82 cm (average age: 48.4 years). Three recurrent cases (3.6%, 3/83) were developed among them, but not significantly more prevalent than T1 (3.8%, 17/447). Even though small not enough to be evaluated, three patient having 1.7 cm, 1.8 cm, and 2 cm PTC in diameter have not reported any recurrence after 111, 129 and 129 month follow up, respectively.

Table 5. Clinicopathologic results of 20 recurred papillary thyroid carcinoma patients

Pt. No.	Age	Sex	CND*	Size (cm)	Tumor site	Tumor location	Tumor encapsulation	Necrosis	Capsule invasion	ETE†	Duration till recurrence (mo)	Recurred site	Duration of follow up (mo)
1	50	Female	Yes	0.8	Left	M [†]	Absent	Absent	Present	Present	14	Central LN [§]	16
2	34	Female	No	1.7	Left	I	Absent	Absent	Absent	Absent	87	Contralateral lobe	145
3	38	Female	No	2.0	Left	U [¶]	Absent	Absent	Absent	Absent	246	Contralateral lobe	253
4	39	Female	No	0.7	Left	M	Absent	Absent	Present	Absent	15	Contralateral lobe	15
5	45	Female	No	0.8	Right	M	Absent	Absent	Present	Present	10	Contralateral lobe	16
6	47	Female	No	1.5	Right	M	Absent	Absent	Present	Absent	38	Contralateral lobe	49
7	51	Female	No	1.0	Right	U	Absent	Absent	Absent	Absent	47	Contralateral lobe	66
8	64	Female	No	0.3	Right	U	Absent	Absent	Absent	Absent	14	Contralateral lobe	64
9	66	Female	No	0.5	Left	M	Absent	Absent	Absent	Absent	9	Contralateral lobe	32
10	25	Female	Yes	0.9	Right	U	Absent	Absent	Absent	Absent	97	Contralateral lobe	99
11	48	Female	Yes	0.7	Left	M	Absent	Absent	Present	Absent	8	Contralateral lobe	55
12	58	Female	Yes	0.8	Left	L**	Absent	Absent	Present	Present	13	Contralateral lobe	13
13	44	Female	No	1.5	Left	U	Absent	Absent	Absent	Absent	29	Contralateral lobe	54
14	53	Female	No	1.3	Right	M	Absent	Absent	Absent	Absent	51	Ipsilateral lateral LN Contralateral lobe	74
15	60	male	No	0.5	Right	M	Present	Absent	Absent	Absent	18	Contralateral lobe bone	42
16	45	Female	No	1.3	Left	M	Absent	Absent	Absent	Absent	24	Contralateral lobe Contralateral lateral LN	49
17	26	Female	No	2.0	Right	U	Absent	Absent	Absent	Absent	21	Ipsilateral lateral LN	40
18	31	Female	No	0.8	Left	U	Absent	Absent	Present	Absent	57	Ipsilateral lateral LN	62
19	33	Female	No	1.3	Right	L	Absent	Absent	Present	Absent	24	Ipsilateral lateral LN	79
20	37	Female	No	1.7	Right	U	Present	Absent	Present	Absent	29	Ipsilateral lateral LN	106

*CND = central lymph node dissection; †ETE = extrathyroidal extension; ‡M = mid; §LN = lymph node; ||I = isthmic; ¶U = upper; **L = lower.

DISCUSSION

This study mainly focused on the role of CND after LI in patients having PTC measuring less than 2 cm in maximum diameter among 530 patients, which showed no significant differences in recurrence. Tumor size was the only significant clinical factor that demanded recurrence risk ($P < 0.001$), even after regrouping patients as PTC vs. PTMC ($P = 0.006$).

PTC is known to disseminate most frequently into regional lymph node, including central lymph nodes.(7,8) There still are controversial issues about pros and cons of routine CND to decrease recurrences. Scheumann et al.(9) insisted that routine CND might improve survival and recurrence rate by decreasing cervical lymph node metastasis in younger patients, male, or T1~T3 cancers. Tisell et al.(10) reported improved survival after microdissection including surrounding fatty tissue and cervical lymph node as far as possible. Sywak et al.(11) showed significant decrease of thyroglobulin after total thyroidectomy with ipsilateral CND, compared to total thyroidectomy only.

On the other hand, there have been reports not recommending routine CND due to increasing post-operative complications but no positive effects on patients' prognosis. Roh et al.(12) warned that total thyroidectomy along with CND significantly decreased serum parathyroid hormone while no influence on the recurrence rate, Cavicchi et al.(13) isolated CND as the only cause provoking transient hypocalcemia postoperatively, and claimed routine CND not backed by robust oncologic data of improving survival and recurrence was not sound. Lee et al.(14) recommended safer unilateral CND instead of bilateral one, according to the fact that, in case of 2 cm or less-sized PTC, bilateral CND promoted hypoparathyroidism while no influence on serum thyroglobulin level.

According to the 2007 NCCN guidelines,(15) there is no remark on the prophylactic CND, while suggestions on the lymphatic dissections in cases of clinically palpable lymph nodes or FNAC-verified lymphatic metastasis. After

revision in 2009, there seems no major changes on the previous one, except prophylactic lymph node dissection can be considered after thorough discussion with patients on the possible complication such as hypoparathyroidism.(3)

But, there is major setback on the CND by the recent ATA guidelines. In 2006, ATA mentioned to consider routine CND aggressively in case of PTC.(6) However, in 2009, they concluded prophylactic CND had no positive impact on the survival while increasing complications thereafter, total thyroidectomy and therapeutic CND, not prophylactic, could be followed after recurrence confirmation. And prophylactic CND was recommended ipsilaterally or bilaterally in cases of advanced PTC such as T3 or T4 by TNM classification. Noticeably, ATA claimed to omit prophylactic CND in T2 thyroid cancer.(2)

In our study population, most patients belong to T1 cases (84.33%, 447/530), and there was no significant influence of CND on recurrence. Therefore, selective CND - not prophylactic - may be applied for patient having less than 2 cm-sized PTC or PTMC, especially.

According to our results, cross analysis revealed PTMC was the determining factor on the recurrence compared to the PTC, but produced no significant differences by Kaplan-Meier survival curve. This might be relatively short follow up period and small number of patients to yield significant differences in survival in this population.

In our series, mean follow-up period was 27.37 months and the range was 1~253 months. It was about short to describe the recurrence rate in PTC patients. We reclassified total patients in this study to three groups: follow-up period was more than 12 months ($n=367$), 18 months ($n=272$) and 24 months ($n=234$). The recurrence rate was 5.4% (20/367), 5.8% (16/272) and 6.8% (16/234) in the group of follow-up period more than 12 months, 18 months and 24 months, respectively. As expected, the factor related with recurrence was only tumor size in the follow-up period more than 12 months, 18 months and 24 months. Therefore, the length of follow-up period did not influence on the results of this study.

There is increasing body of assertion on favoring total

thyroidectomy instead of LI for PTCs measuring between 1~2 cm in maximum diameter, while LI can be applied for PTMC otherwise not risky. By the way, NCCN suggests LI is ample, even in case of PTC less than 4 cm in diameter without risk factors, and completion thyroidectomy may be followed after confirmation of aggressive histology, macroscopic multifocal disease, positive margin, cervical lymph node metastasis or extrathyroidal extension.(3) By our non-published data due to irrelevant point of view, there was no differences in recurrence by comparing total thyroidectomy and LI in patients having less than 2 cm-sized PTC (P=0.242).

In conclusion, according to our data, we failed to find any relevant role of CND to prevent recurrence either local or regional in case of no lymph node metastasis after CND for patients having PTC measuring 2 cm or less. Even though, longer follow up and larger patient population should be required to get the definite answer, we don't think prophylactic CND is mandatory for all cases of PTC having less than 2 cm-sized index tumor.

If possible, prospective randomized clinical trial should be followed in the very near future to answer these questions yet to be elucidated to offer patients suffering relatively early phase PTC maximum safety and oncologic outcome.

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