

Original Article

Is Routine Central Neck Dissection Necessary for the Treatment of Papillary Thyroid Microcarcinoma?

Se Jun Choi, MD¹ · Tae Yong Kim, MD² · Jong Cheol Lee, MD⁶ · Young Kee Shong, MD, PhD²
 Kyoung-Ja Cho, MD, PhD³ · Jin Sook Ryu, MD, PhD⁴ · Jeong Hyun Lee, MD, PhD⁵
 Jong-Lyel Roh, MD, PhD¹ · Sang Yoon Kim, MD, PhD¹

Departments of ¹Otolaryngology, ²Internal Medicine, ³Pathology, ⁴Nuclear Medicine, and ⁵Radiology, Asan Medical Center, University of Ulsan College of Medicine, Seoul; ⁶Department of Otolaryngology, Ulsan University Hospital, University of Ulsan College of Medicine, Ulsan, Korea

Objectives. It remains unclear as to whether routine central neck dissection (CND) is necessary when performing surgery to treat patients with papillary thyroid microcarcinoma (PTMC). To determine the necessity for routine CND in PTMC patients, we reviewed the clinicopathologic and laboratory data of the patients of PTMC.

Methods. Between September 2001 and July 2005, 101 patients with PTMC and clinical N0 disease were retrospectively reviewed. The study cohort was divided into groups: the total thyroidectomy plus CND group (the CND group, N=48) and the total thyroidectomy without CND group (the no CND group, N=53). The serum stimulated thyroglobulin (Tg) levels were measured after surgery and prior to radioactive iodine ablation therapy (RAI) and at 6-12 months after RAI. Pathology, the Tg levels and recurrence data were compared between the 2 groups.

Results. Central nodal metastases were found in 18 of the 48 CND patients (37.5%). The incidence of Tg levels >5 ng/mL at RAI was higher in the no CND patients and in the 18 node-positive CND patients compared with the 30 node-negative CND patients (22-24% vs. 3%, respectively, $P=0.020-0.058$). The difference when performing a similar comparison using a >2 ng/mL Tg threshold level showed no significance (10-11% vs. 4%, respectively, $P>0.1$). Two of the no CND patients and one node-positive CND patient had recurrences in the thyroid bed or lateral neck during a mean follow-up of 24 months.

Conclusion. The data showed that occult metastasis to the central neck is common in PTMC patients. A CND provides pathologic information about the nodal metastases, and it potentially provides guidance for planning the postoperative RAI. However, the long-term benefit of CND on recurrence and survival remains somewhat questionable.

Key Words. Papillary microcarcinoma, Central compartment, Neck dissection, Neoplasm metastasis, Thyroglobulin

INTRODUCTION

Papillary thyroid microcarcinoma (PTMC) is defined as a papillary thyroid carcinoma that's equal to or less than 1.0 cm at the greatest dimension according to the World Health Organization classification system for thyroid tumors (1). The prevalence of

PTMC in the general population with no thyroid disease is reportedly high at 3-36%, according to autopsy studies (2-4). The majority of PTMCs are not palpable and show an asymptomatic course (5). High-resolution thyroid ultrasonography and fine-needle aspiration cytology (FNAC) under ultrasound guidance have recently enabled making an accurate diagnosis of PTMC, which may explain why the reported incidence of PTMC is increasing (6). Although PTMC generally has a favorable prognosis, the tumor may show locoregional recurrence and distant metastases (7-10). For PTMC patients, the reported incidence of lymph node metastasis is as high as 40%, and these occur mainly in the central compartment of the neck (2, 3, 11). However, the prognostic factors that can differentiate silent PTMC from potentially aggressive PTMC remain unclear.

One of the major issues for the treatment of PTMC is whether central neck lymph node dissection (CND) should be routinely

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 • Se Jun Choi and Tae Yong Kim are equally contributed as first author.
 • Corresponding author : **Sang Yoon Kim, MD, PhD**
 Department of Otolaryngology, Asan Medical Center, University of Ulsan College of Medicine, 388-1 Pungnap-2dong, Songpa-gu, Seoul 138-736, Korea
 Tel : +82-2-3010-3715, Fax : +82-2-489-2773,
 E-mail : sykim2@amc.seoul.kr
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performed during the initial operation. While CND is not generally performed due to the excellent prognosis of PTMC, some reports have recommended performing routine CND even in PTMC patients with no clinical nodal metastases (12, 13).

The present study reviewed the surgery, pathology, laboratory and follow-up data of 101 patients who underwent surgery for PTMC. In order to determine the clinical necessity of performing CND in PTMC patients, the patients were analyzed in terms of those who underwent CND (CND) and those who did not (no CND).

MATERIALS AND METHODS

Patient population and study design

The clinical data was reviewed on 106 PTMC patients who underwent total thyroidectomy between September 2001 and July 2005. The pathology of all the patients were papillary carcinoma, as indicated by fine needle aspiration cytology that was guided by high-resolution ultrasonography, and the aspiration pathology was confirmed by the surgical pathology. Preoperative evaluation included taking a clinical history and a physical examination, thyroid function tests and radiography of the thorax and ultrasonography. The ultrasonographic examinations were performed preoperatively by the same experienced radiologist (J.H.L) in order to evaluate lymph node metastasis. Five patients who were preoperatively suspected of having cervical lymph node metastasis and who underwent therapeutic neck lymph node dissection were excluded from the study. Thus, 101 patients with primary tumor sizes ≤ 1.0 cm and no preoperative evidence of nodal metastases were finally included in the study.

For analysis, the patients were divided into 2 groups: the total thyroidectomy without CND group (the no CND group, N=53) and the total thyroidectomy plus CND group (the CND group, N=48) (Table 1). The study cohort was not randomized and the decision to perform CND was made by both the surgeon and the patient. The pathology, laboratory findings and recurrence were compared between the two groups. This study was reviewed and approved by the Institutional Review Board of the Asan Medical Center and informed consent was waived.

Central node dissection

CND was carried out in a conventional manner and microdissection methods were not used (14). Node clearance was performed cranially to both superior thyroid arteries and the pyramidal lobe, caudally to the innominate vein, laterally to the carotid sheaths and dorsally to the prevertebral fascia (5). The thymus was commonly preserved by separating it from the central nodes. The central compartment was divided into 4 node sites: the pretracheal site, the ipsilateral site, the contralateral paratracheal site and the superior mediastinal site below the sternal notch. Particular attention was given to identifying the parathyroid glands, and

Table 1. The clinical characteristics, pathologic findings and complications of the PTMC patients who underwent (the CND group) or did not undergo (the no CND group) routine central neck dissection*

Variables	no CND group (N=53)	CND group (N=48)	P-value [†]
Gender (male:female)	11:42	6:42	0.30
Mean age (years)	48 \pm 9.9	52 \pm 12.0	0.10
Mean size of primary tumor (mm)	7.3 \pm 2.3	6.8 \pm 2.1	0.18
Multifocality (single:multiple)	12:41	15:33	0.37
Extrathyroidal extension	31/53	22/48	0.24
Metastases to the central neck	N/A	18/48	
Transient hypocalcemia (%)	6 (11.3)	8 (16.7)	0.78
Permanent hypocalcemia (%)	1 (1.9)	0	
Transient vocal cord palsy	0	1 (2.1)	0.48

PTMC: papillary thyroid microcarcinoma; CND: central neck dissection.

* None of the patients had evidence of cervical nodal metastases prior to surgery.

[†] Fisher's exact test except for age and the primary tumor size (t-test).

parathyroid autotransplantation was carried out as required, not on principle.

Observation of the pathology and complications

The pathology was carefully reviewed with focusing on the primary tumor size and multifocality, extrathyroidal extension and lymph node metastases. The prevalence of central nodal metastases was obtained from the CND patients. The medical records regarding the surgical complications were thoroughly reviewed. Hypocalcemia was defined as the need for exogenous calcium replacement in order to maintain a normal range of serum total calcium (8-10.4 mg/dL) or to eliminate the clinical signs and symptoms of hypocalcemia. Hypocalcemia was considered permanent when calcium replacement was necessary for longer than 12 months.

Measurement of serum thyroglobulin and the follow-up

All the patients received radioactive iodine ablation therapy (RAI) with 2.78-5.55 GBq ¹³¹I at 5-6 weeks after surgery. Prior to RAI, the serum thyroid-stimulating hormone (TSH) level was elevated to >30 mU/L, and then the serum levels of stimulated Tg (ablation-Tg) and anti-Tg antibody were measured. A whole body scan (WBS) using 148 MBq ¹³¹I was performed at 5-7 days and at 6-12 months after RAI with a simultaneous measurement of the serum stimulated Tg (control-Tg). The serum Tg levels were measured using a solid phase two-site immunoradiometric assay kit (ELSA-hTG[®], Schering-CIS Bio International, Gif/Yvette, France) as previously described (15). The detection limit of thyroglobulin was 1.0 ng/mL. The anti-Tg levels were measured using radioligand assays (HENNING test anti-Tg; BRAHMS Diagnostica, Berlin, Germany). Anti-Tg values above 100 U/mL were considered positive. When the control-Tg level was above 2 ng/mL, then neck ultrasonography with or without fine needle aspiration cytology was performed to localize the potential-

ly malignant thyroid lesions.

Statistical analysis

The *t*-test was used to analyze the mean differences of the pathologic findings and the other clinical parameters between the groups. Fisher's exact test or χ^2 test was used to investigate differences among the categorical data. A *P*-value of less than 0.05 was deemed to indicate a significant difference. SPSS software (version 12.0, SPSS, Inc., Chicago, IL, USA) was used for analysis of the data.

RESULTS

The study cohort consisted of 17 men and 84 women, with a mean age of 49.8 years (range: 23 to 76 years) (Table 1). The CND and no CND groups were similar in terms of gender and the age distribution. The mean follow-up time after surgery was 24.4 months (range: 13-55 months).

Complications and the pathologic findings

Both the CND and no CND groups had similar complication rates ($P>0.1$). The overall incidence of hypocalcemia was 15 of 101 patients (14.9%), of whom only one patient had permanent hypocalcemia. Transient vocal cord palsy occurred in only one CND patient. Other complications (e.g., bleeding, hematoma and seroma) were not noted in either group (data not shown). No pathologic difference was found between the groups. The mean size and the presence of multifocality and an extrathyroidal extension of the primary tumors were the same for both groups. For the CND group, 18 of 48 patients (37.5%) had central nodal metastasis.

Serum thyroglobulin levels and recurrence

The levels of ablation-Tg and control-Tg were compared between the no CND patients and the CND patients with or without central nodal metastases (Fig. 1). Three no CND patients were excluded from the Tg analyses due to positive anti-Tg antibody results (>100 U/mL). Of the remaining 50 no CND patients, 12 (24.0%) had ablation-Tg levels >5 ng/mL, 11 (22.0%) had levels from 2-5 ng/mL, and 27 (54.0%) had levels <2 ng/mL (Fig. 2). The 48 CND patients were analyzed as those with ($N=18$) or without ($N=30$) pathologic central nodal metastases. While the proportion of patients with a serum stimulated ablation-Tg level >5 ng/mL appeared to be higher in the node-positive compared to the node-negative group (4/18 vs. 1/30, respectively), this difference did not reach statistical significance ($P=0.058$). The same analysis with using an ablation-Tg threshold level of <2 ng/mL showed the proportion of such patients was similar in both the node-positive and node-negative groups (12/18 vs. 24/30, respectively, $P=0.325$).

On the analyses of the control-Tg levels, 4 no CND patients and 3 CND patients were excluded due to positive anti-Tg levels

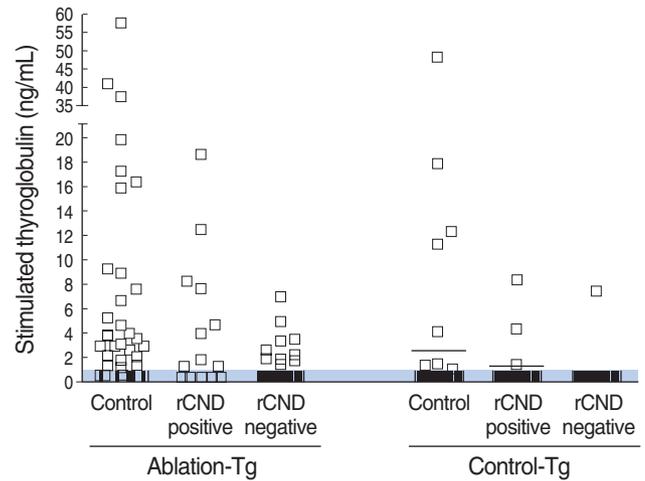


Fig. 1. Serum TSH-stimulated Tg levels in patients either undergoing (CND) or not undergoing (no CND) central node dissection (CND). The ablation- and control-Tg levels were measured prior to radioactive iodine therapy (RAI) and at follow-up 6-12 months after RAI, respectively. The mean Tg levels were higher in the no CND and node-positive CND patients than in node-negative CND patients: ablation-Tg, 5.780 and 3.367 ng/mL vs. 1.059 ng/mL, $P=0.054$; control-Tg, 2.078 and 0.904 ng/mL vs. 0.447 ng/mL, $P=0.319$.

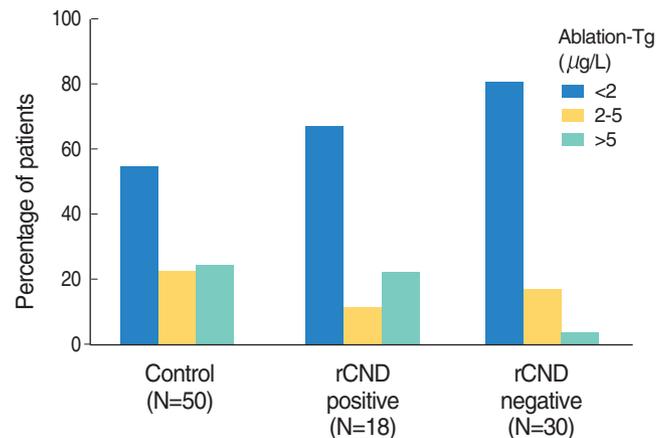


Fig. 2. Serum TSH-stimulated Tg levels prior to radioactive iodine therapy. The ablation-Tg levels were categorized as >5.0 ng/mL, 2.0-5.0 ng/mL and <2.0 ng/mL. The central neck dissection (CND) patients were analyzed as those with or without occult metastases to the central neck compartment.

(>100 U/mL). The proportion of patients with serum stimulated control-Tg levels >2 ng/mL did not significantly differ between the no CND or the node-positive CND patients and the node-negative CND patients (5/49 or 2/18 vs. 1/27, respectively, $P>0.1$) (Fig. 3).

Three patients experienced recurrence during follow-up (2 no CND patients and 1 node-positive CND patient), as confirmed by ultrasonography-guided fineneedle aspiration cytology. The 2 no CND patients had recurrences in the thyroid bed and lat-

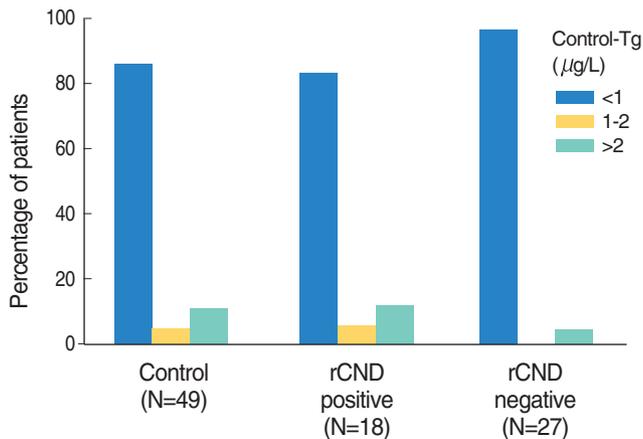


Fig. 3. The serum TSH-stimulated Tg levels at follow-up 6-12 months after radioactive iodine therapy. The control-Tg levels were categorized as >2.0 ng/mL, $1.0-2.0$ ng/mL and <1.0 ng/mL. The central neck dissection (CND) patients were analyzed as those with or without occult metastases to the central neck compartment.

eral neck. The 1 node-positive CND patient had a recurrence in the lateral neck. The ablation-Tg levels and control-Tg levels of all the patients with recurrences were as high as >8.0 ng/mL.

DISCUSSION

The present study found that CND was not associated with any increase in postoperative complications. The incidence of hypocalcemic was the same for both CND and no CND groups, suggesting that exploration of the central neck compartment did not lead to increased damage to the parathyroid glands during CND. These findings are in disagreement with those of others researchers who reported that while CND was not associated with an increased risk of postoperative vocal fold paralysis, it was linked to a higher rate of transient and permanent hypoparathyroidism (16, 17). Such findings have resulted in CND not being routinely used in all PTMC patients. However, the current study shows that CND can be safely performed by an experienced surgeon and this procedure does not increase the risk of surgical morbidity.

In the current study, occult metastasis to the central neck compartment was found in 37.5% of the CND patients with no clinical nodal metastasis, which is consistent with the other recent reports (5, 18). The pathologic finding of PTMC having a high proclivity for regional metastases seems to justify performing routine CND in these patients. A recent study of 600 PTMC patients who underwent CND found there was no significant difference for disease-free survival between the patients who were positive (43%) or negative (57%) for central nodal metastasis (18). Another study asserted that nodal recurrence did not differ between the prophylactic dissection group and the no-dissection group, prophylactic CND for PTMC is not beneficial to the

patients with no palpable lymphadenopathy.

A major issue of PTMC treatment is the prognostic value of microscopic lymph node involvement. Measurement of the serum TSH-stimulated Tg levels is an important method for detecting the presence of residual or recurrent malignant thyroid tissue during follow-up. The meaning of the Tg levels at RAI is still debatable because the thyroid remnants and untreated occult metastasis contribute to Tg synthesis and therefore, the increased Tg levels. However, a prior report suggested that the ablation-Tg levels were well correlated with the control-Tg levels, and that levels >2.0 ng/mL were highly associated with persistent or recurrent disease in the low-risk patients with well-differentiated thyroid carcinoma (15). Therefore, we used both the ablation-Tg and control-Tg levels for predicting recurrences. The ablation-Tg levels appeared to be higher in the controls or the CND patients with nodal metastases than that in the CND patients without nodal metastases. In addition to the pathologic information on nodal metastases in PTMC patients, this may also suggest a role for CND in planning RAI after surgery.

Recent studies have investigated whether the control-Tg values can predict recurrent and persistent disease (19, 20). The current study found that control-Tg levels did not differ among the 3 groups, and that the recurrence rate was very low. Moreover, no recurrence was found in any of the CND patients without occult nodal metastasis, suggesting that this group has a good prognosis and there is no need for high-dose RAI. Thus, CND may have a role in determining the plan for postoperative RAI and also the patient's prognosis.

The present study data allowed us to investigate whether RAI was sufficient to remove occult metastasis. For the control patients, 44.0% had a stimulated Tg level above 2 ng/mL prior to RAI, while only 10.2% were above 2 ng/mL at 6-12 months after RAI. This result suggests that RAI may be an effective method for ablating the remnant thyroid tissue or disease. However, the potential benefits of RAI on lowering the disease recurrence rate and the mortality rate of PTMC patients remains as a controversial issue (9, 21-23), and no randomized, controlled clinical trials have yet been performed on a large number of patients. Furthermore, RAI has side effects, including radiation sialadenitis in up to 40% of patients, with the incidence linked to the dose of radioiodine (24). The recent data suggests that low-risk patients with PTMC do not benefit from RAI (23). Thus, CND may help discriminate between the patients with and without PTMC-associated metastatic neck diseases and so this can abrogate the necessity of high-dose RAI for the low-risk patients.

The present study may have been limited by its retrospective non-randomized design. The decision to perform a CND may have been skewed by the surgeon's preference. However, the general demographic and pathologic data were comparable between the control and CND groups. The study also included more than 100 PTMC patients with a clinical N0 neck, which is a large number of patients and it is more than sufficient for making be-

tween-group comparisons. A relatively short follow-up period may also have been a limitation, and it may have affected the findings regarding recurrence or survival. The present data showed that the serum TSH-stimulated Tg levels were predictive of recurrence, and now a larger study with a longer follow-up period is warranted to confirm our results.

CONCLUSION

The present study found that occult metastasis to the central compartment is a common event in PTMC patients. A CND provides pathologic information on nodal metastases, which may assist the postoperative RAI planning. It appears that the stimulated Tg levels at RAI and follow-up may help predict recurrence, and while this observation did not reach statistical significance in this study, we believe it may reach significance in a larger study. The long-term benefit of CND on recurrence and survival ultimately remains questionable. However, our present findings indicate that these questions may be answered by a longer follow-up of these patients.

CONFLICT OF INTEREST STATEMENT

The authors have no conflicts of interest concerning this research.

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