

Prophylactic Central Compartment Node Dissection for Papillary Thyroid Carcinoma: Complication and Outcome

Jun Soo Jeong, M.D., Jin Young Lee, M.D., Sang Jeon Lee, M.D., Sung-Soo Koong, M.D.¹
and Jin-Woo Park, M.D.

Departments of Surgery and ¹Internal Medicine, College of Medicine, Chungbuk National University, Cheongju, Korea

Purpose: Prophylactic central compartment node dissection is gaining acceptance in the treatment of papillary thyroid carcinoma (PTC). However, its benefits remain controversial. The aim of study was to evaluate the effects of prophylactic central compartment node dissection on the complication rate and the short-term disease-free survival rate.

Methods: Our treatment strategy for PTC without clinical evidence of lymph node metastasis has been changed from total thyroidectomy alone (group I) to total thyroidectomy with prophylactic central compartment node dissection (group II) since January 2007. Before and after 2007, 70 consecutive patients were selected in each group.

Results: The average age of patients was 46.3±11.8 years. Average follow-up period was 51.9±10.9 months. The average size of maximum diameters of the tumors was 1.3±0.8 cm. Lymph node metastasis was identified in 22.9% of patients in group II. Recurrent laryngeal nerve injury occurred in one patient in each group. Temporary and permanent hypoparathyroidism occurred in 32.9% and 2.9% in group I, 40.0% and 7.1% in group II respectively (P=0.483 and P=0.441, respectively). Locoregional recurrences developed in seven patients in group I. Fifty month disease-free survival rate was 90.0% and 100% in group I and group II, respectively (P=0.0078).

Conclusion: Prophylactic central compartment node dissection did not seem to increase the risk of recurrent laryngeal nerve injury, but may increase the risk of temporary and permanent hypoparathyroidism. Prophylactic central compartment node dissection decreased the risk of locoregional recurrences, especially in central compartment. However, the size of metastatic lymph nodes in central compartment in the present study was relatively small and their clinical implication remains to be evaluated. (Korean J

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Key Words: Prophylactic central compartment node dissection, Papillary thyroid cancer, Complication, Hypoparathyroidism, Disease free survival

INTRODUCTION

In head and neck cancers, thyroid cancer has the highest frequency of occurrence and is the most common malignant tumor among endocrine tumors. Papillary thyroid cancer is the most common type of thyroid cancer and accounts for 87.8% of all thyroid cancers in Korea.(1) Lymph node metastasis is common in papillary thyroid cancer, and it spreads gradually from the central neck lymph node to the lateral neck lymph node. The frequency of clinically diagnosed lymph node metastasis is approximately 10 to 20%.(2,3) but when lymph node micro-metastasis that cannot be identified through physical examinations or imaging studies are included, the frequency rises from 35% up to 80%.(4) However, there is still much debate regarding the influence of lymph node metastasis on survival rate and relapse so there are a number of different views about indications for neck lymph node dissection and its range.

The central compartment lymph node is the area where lymph node metastasis first occurs in papillary thyroid cancer. Surgeons who assert that prophylactic central compartment lymph node dissection is necessary although lymph node metastasis has not been confirmed clinically base their arguments on the facts that central compartment lymph node metastasis is common; it is hard to diagnose before surgery, and in the case of relapse, a second operation has a high risk of damaging the recurrent laryngeal nerve or occurring hypoparathyroidism.(5,6) On the other hand, there are many assertions that central compartment lymph node dissection should only be done when metastasis is confirmed clinically since even though the rate of micro-metastasis may be high,

Correspondence: Jin-Woo Park, Department of Surgery, Chungbuk National University College of Medicine, 62, Kaesin-dong, Cheongju 360-763, Korea
Tel: +82-43-269-6033, Fax: +82-43-266-6037
E-mail: webjwpark@chungbuk.ac.kr

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the clinical rate of recurrence is only 7~15% and does not greatly affect the survival rate.(7)

The value of prophylactic central compartment lymph node dissection must be taken into consideration of various aspects such as whether it can reduce the danger of relapse or death through surgery, whether there is any increase in complications, whether it is cost-effective for the patient, and whether it helps psychologically. The aim of this paper was to investigate the usefulness of prophylactic central compartment lymph node dissection based on complications that can occur after surgery such as postoperative bleeding, recurrent laryngeal nerve injury, hypoparathyroidism, and disease free survival during follow-up period.

METHODS

1) Selection of subjects and subject groups

Out of the 237 patients who underwent an operation for papillary thyroid cancer at our hospital during November 2005 to December 2007, 196 patients who did not have lymph node metastasis in their preoperative examination were selected. From these, 4 patients who were difficult to follow-up and monitor as outpatients and 52 who received surgery during the transition period of the surgical policy were excluded from the study. The study was done on 140 patients, in which 70 patients who underwent total thyroidectomy before 2007 were categorized as Group I and 70 patients who underwent total thyroidectomy and prophylactic central compartment lymph node dissection after 2007 were categorized as Group II. The mean age of the patients at the time of surgery was 46.3 (16~77), and the male to female ratio was 1 : 7.75 (16 : 124).

2) Treatment and follow-up

Thyroidectomy was performed as close as possible to the thyroid capsule. By this method, the superior and inferior thyroidal arteries were preserved so that circulation to the parathyroid was maintained. Then, autotransplantation was done after preserving or dissecting all distinguishable parathyroids. In group II, central compartment lymph node dissection was done ipsilateral to the papillary thyroid cancer lesions as a preventive measure. When the lesions were bilateral or were at the isthmus, bilateral central compartment lymph node dissection was done.

All patients underwent thyroid function test and neck sonography before surgery and after surgery. Local recurrence or distant metastasis was monitored by neck sonography, serum thyroglobulin, iodine whole body scan and chest radiographs in follow-up observations. Disease free survival was defined as no evidence of local recurrence or distant metastasis by the neck so-

nography, serum thyroglobulin, iodine whole body scan, and chest radiographs from the day of surgery to the most recent date when the follow-up results were checked. In the case of recurrence, disease free survival was defined as time interval from the day of surgery to the day of recurrence that was confirmed either by aspiration cytology and imaging study.

The occurrences of postoperative bleeding, recurrent laryngeal nerve injury, and hypoparathyroidism were reviewed by medical records including operational records and laryngoscopic results after surgery. Hypoparathyroidism was defined as hypocalcemic symptoms in postoperative period, or even without symptoms, the total concentration of calcium level in two days after surgery was less than 8 mg/dl or ionized calcium level was less than 4 mg/dl. When continual calcium supplementation was necessary for more than 6 months after surgery to diminish clinical symptoms or maintain normal calcium levels, it was defined as permanent hypoparathyroidism.

To exclude other factors that may influence the results after treatment, information such as the size of the lesions, extrathyroidal extension, lymph node metastasis, bilaterality, or multifocality as well as the sex and age of the patients were examined for any significant differences between the subject groups.

3) Statistical analysis

SPSS 12.0 (2003 SPSS Inc. Chicago, Illinois, USA) was used for statistical analysis. Disease free survival was analyzed using a Kaplan-Meier survival curve, and comparative analysis of the characteristics of the subject groups and recurrences according to each factor were analyzed using the t-test and Chi-square test (Fisher's exact test) with $P < 0.05$ considered as statistically significant.

RESULTS

1) Characteristics of the subject groups

The mean age and sex of each group was not significantly different: Group I, mean age 44.7 ± 12.1 (16~77) with a 1 to 9 ratio of men to women; Group II, mean age 47.9 ± 11.4 (24~77) with a 1 to 6.8 ratio of men to women. According to the pathological reports after surgery, the size of the main lesion, extrathyroidal extension, bilaterality, multifocality were not significant difference in each group. In risk classification according to MACIS scores which evaluate the prognosis depending on the local recurrence, the age of the patient, the completeness of the surgery, local invasion status, and the size of the tumor, 92.9% (65/70) of Group I and 90.0% (63/70) of Group II were considered a low risk, while 7.1% (5/70) of Group I and 10.0% (7/70) of Group

II were considered a high risk (P=0.764).

Radio-active iodine ablation was done on 75.7% (53/70) of Group I and 87.1% (61/70) of Group II (P=0.127). The length of the follow-up period was 57.46±12.10 months for Group I and 46.33±5.49 months for Group II. Lymph node metastasis occurred in 22.9% (16/70) of Group II (Table 1).

Table 1. Demographics and clinicopathological characteristics of patient groups

		Group I n=70 (%)	Group II n=70 (%)	P value
Age (years)	Average	44.7±12.1	47.9±11.4	0.235
	<45	36 (51.4)	28 (40.0)	
	≥45	34 (48.6)	42 (60.0)	
Sex	Female	63 (90.0)	61 (87.1)	0.791
	Male	7 (10.0)	9 (12.9)	
Size (cm)	Average	1.35±0.89	1.28±0.85	0.864
	≤1	41 (58.6)	39 (55.7)	
	>1	29 (41.4)	31 (44.3)	
Extrathyroidal extension		25 (35.7)	36 (51.4)	0.088
Bilaterality		13 (18.6)	17 (24.3)	0.537
Multifocality		16 (22.9)	21 (30.0)	0.444
MACIS*	Low risk	65 (92.9)	63 (90.0)	0.764
	High risk	5 (7.1)	7 (10.0)	
LN metastases			16 (22.9)	
RI [†] ablation		53 (75.7)	61 (87.1)	0.127
F/U (Months)		57.46±12.10	46.33±5.49	

*MACIS score (distant metastasis, patient age, completeness of resection, local invasion, and tumor size); MACIS score=3.1 (if age <40 years) or 0.08×age (if age ≥40 yrs); +0.3×tumor size (cm maximum diameter); +1 (if incompletely resected)+1 (if locally invasive)+3 (if distant spread); If MACIS score <6=low risk, ≥6=high risk; [†]Radioactive-iodine ablation criteria: maximal diameter of the tumor >1 cm, extrathyroidal extension, multifocality, or Lymph node metastasis (+).

2) Complications after surgery

There was no postoperative bleeding in both groups. There was one case of recurrent laryngeal nerve damage in each group. The temporary and permanent hypocalcemia seems to increase in group 2, but it was not statistically significant (P=0.483, P=0.441; respectively). Two patients out of the 5 in Group II recovered from the hypocalcemia within one year after surgery (Table 2).

3) Recurrence and duration of disease free survival

Recurrence only occurred in 7 patients (10%) from Group I. The mean value of the time period from surgery to recurrence was 20.43±16.38 months. 5 patients of all recurrence cases were local lymph node metastasis in the central compartment area and another two cases were lateral neck node metastasis. The mean size of metastatic lymph nodes was 1.13±0.5 cm (Table 3). Disease free survival rate was 90% in Group I and 100% in Group II (P=0.0078) (Fig. 1).

When the 7 cases of recurrence were examined, all the cases

Table 2. Postoperative complications according to the patient groups

	Group I n=70 (%)	Group II n=70 (%)	P value
Post OP. bleeding	0	0	Not significant
RLN* injury	1 (1.4)	1 (1.4)	Not significant
Hypoparathyroidism			
Transient	23 (32.9)	28 (40.0)	0.483
Permanent	2 (2.9)	5 (7.1) [†]	0.441

*Recurrent laryngeal nerve; [†]In Total thyroidectomy with prophylactic central compartment node dissection group, two of 5 patients recovered from hypoparathyroidism 1year after operation.

Table 3. Summary of recurrence cases

Age	Sex	Tumor size (cm)	ETE*	Time to recurrence (months)	Recurrence site	LN [†] size (cm)	Management
38	F	0.8	(-)	6	Central compartment	0.8	Central compartment node dissection Central & Rt. lateral
31	F	4	(+)	8	Rt. level IV LN	1.8	Compartment node dissection
33	F	3	(-)	9	Central compartment	1	Transfer
41	F	2	(+)	10	Central compartment	1.8	Transfer
26	M	1	(-)	25	Central compartment	0.5	RI therapy
44	F	2.2	(+)	40	Lt. level IV LN	1.2	Central & Lt. lateral compartment node dissection
16	F	1.8	(+)	45	Central compartment	0.8	Central compartment node dissection

*Extrathyroidal extension; [†]Maximum metastatic lymph node size.

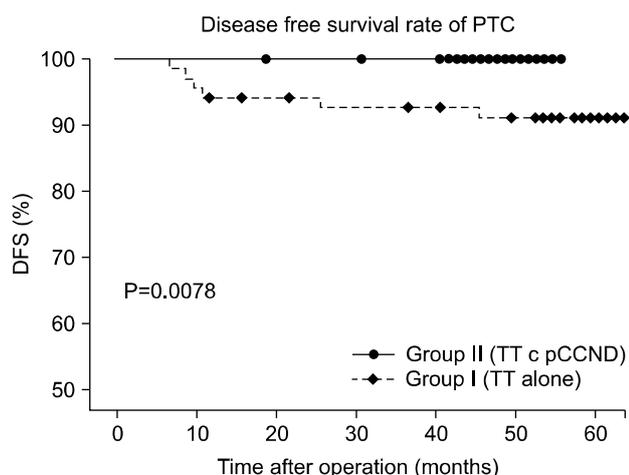


Fig. 1. Disease free survival rate of papillary thyroid cancer according to patient groups.

were patients under 45 years of age (P=0.011) with 6 females and 1 male (P=0.538). As expected, the size of tumor, extra-thyroidal extension, and radio-active iodine ablation were more frequently noted at presentation (P=0.118, P=0.239, P=0.183; respectively). Most of recurrence cases had unilateral lesion (P=0.759) and solitary lesion (P=0.569). There were no clinicopathological factors showing a statistically significant correlation to recurrence except age (Table 4).

DISCUSSION

Lymph node metastasis in papillary thyroid cancer is common, and the central compartment lymph nodes are the most common area of metastasis.(8) The frequency of lymph node metastasis can be different depending on the method of diagnosis. Approximately 10~15% of patients who undergo surgery for thyroid cancer can be diagnosed through physical examination before surgery, but when micro-metastasis is included, the frequency is as high as 80%. After surgery neck lymph node metastasis is the most common type of recurrence, and it consists of about 75% of recurrence cases. However, the influence of lymph node metastasis on the prognosis and recurrence has been under debate.(9,10) Mazzaferri(11) reported that lymph node metastasis does not affect the survival rate or recurrence rate of patients with papillary thyroid cancer, but recently, there have been reports that contradict this view. There are reports that state central compartment lymph node metastatic remnant from the first surgery causes local recurrence or distant metastasis(12-14) and that lymph node metastasis is one of the factors of poor survival.(15) Lundgren et al.(15) report that when central neck lymph node metastasis is suspected, removing not only the enlarged lymph node but also

Table 4. Clinicopathologic factors associated with recurrence after total thyroidectomy alone group

		Group I		P value
		Recurrence (-) number (%)	Recurrence (+) number (%)	
Age (years)	<45	29 (46.0)	7 (100)	0.011
	≥45	34 (54.0)	0	
Sex	Female	57 (90.5)	6 (85.7)	0.538
	Male	6 (9.5)	1 (14.3)	
Size (cm)	≤1	39 (61.9)	2 (28.6)	0.118
	>1	24 (38.1)	5 (71.4)	
Extrathyroidal extension	(-)	42 (66.7)	3 (42.9)	0.239
	(+)	21 (33.3)	4 (57.1)	
Multifocality	(-)	48 (76.2)	6 (85.7)	0.569
	(+)	15 (23.8)	1 (14.3)	
Bilaterality	(-)	51 (81.0)	6 (85.7)	0.759
	(+)	12 (19.0)	1 (14.3)	
RI* ablation	(-)	17 (27.0)	0	0.183
	(+)	46 (73.0)	7 (100)	

*Radio-active iodine.

the central compartment lymph nodes adjacent to the lesion and even the opposite lymph node depending on the case can reduce recurrence in the central compartment lymph nodes. However, although curative lymph node dissection should definitely be done for lymph nodes detected before surgery or confirmed through pathological reports, many believe that prophylactic central compartment lymph node dissection is unnecessary.(16)

In our research, from the 70 patients who underwent central compartment lymph node dissection, lymph node metastasis was confirmed in 16 patients (22.9%). Our frequency is comparable to the results in Park et al.,(17) Lee et al.,(18) and Lee et al. (19) who reported lymph node metastasis in 55 patients (21.2%) out of 260, in 55 patients (44.7%) out of 123, and 26.9%, respectively.

Grodski et al.(9) recommended prophylactic dissection of the ipsilateral central compartment lymph node together with total thyroidectomy since there was a high occurrence rate of metastasis in the central compartment lymph node in papillary thyroid cancer. Sywak et al.(20) asserted that if prophylactic central compartment lymph node dissection was done together with total thyroidectomy, the lesion was removed more thoroughly, and post-surgical thyroglobulin levels could be further lowered. Pereira et al.(21) reported that recurrences were significantly reduced in cases that had prophylactic central compartment lymph node dissection done on both sides. Zarneger et al.(22) reported that 25% of thyroid cancer and 50% of recurring thyroid cancer did not respond to radiation therapy. Some argue that the effect of radiation therapy is

not certain on the remaining cancer cells including micro-metastasis after surgery so prophylactic central compartment lymph node dissection should be done.(4) Another reason to argue prophylactic central compartment lymph node dissection is that most recurrence appears in the central compartment lymph node like our research, and in the case of additional surgery, there is a high risk of complications such as recurrent laryngeal nerve injury and hypoparathyroidism.(23) If there is a high possibility of complications from re-operation, it is necessary to make an effort to prevent recurrence in this area by removing all the central compartment lymph nodes in the initial treatment.(24) Our research seems to support this argument because most of all recurrence cases had confirmation of central compartment lymph node metastasis, and recurrence had occurred in cases where radiation therapy had been done after surgery.

Another important fact to consider is whether complications from surgery increase when prophylactic central compartment lymph node dissection is done. The frequency of hypocalcemia after total thyroidectomy is widely reported, in which the occurrence of temporary hypocalcemia is reported as 1.6~50.1% and permanent hypocalcemia as 0~13.8%.(25) In the meta-analysis results of White et al.,(26) the occurrence of permanent hypocalcemia after undergoing central compartment lymph node dissection was reported as 1.4~11.3% and recurrent laryngeal nerve injury at 0~11.5%, and these complications increased when central compartment lymph node dissection was done rather than when only total thyroidectomy was done. In our research, temporary hypocalcemia occurred in 32.9% of the group who underwent only total thyroidectomy and 40% of the group with additional central compartment lymph node dissection, and permanent hypocalcemia was observed in 2.9% and 7.1% of each group. So there was an increase in complications by adding prophylactic central compartment lymph node dissection, but it was not statistically significant. Recurrent laryngeal nerve injury occurred in 1.4% of both groups so there were no differences between them. There could be many reasons for the high rate of temporary or permanent hypoparathyroidism in the group who underwent prophylactic central compartment lymph node dissection in our research. First of all, it was the first year when prophylactic central neck lymph node dissection was done so the technical proficiency of the operating surgeon could be a problem. Second, because hypoparathyroidism was defined by routine measurement of calcium concentration even when there were no symptoms observed.

Factors that influence recurrence in papillary thyroid cancer have not been clearly defined yet. White et al.(26) reported that the age of the patient, size of the tumor, multifocality, and the degree of extrathyroidal extension could be influential. Lee et

al.(18) reported that the size of the tumor was irrelevant, whereas the patient's age, sex, and extrathyroidal extension were related to lymph node metastasis. In addition, Lee et al.(19) reported that extrathyroidal extension and lymph node metastasis were factors that influenced recurrence. In our research, a tendency for recurrence was exhibited by the younger patients ($P=0.011$). But, gender, size of tumor, extrathyroidal extension, multifocality, and bilaterality were unrelated to recurrence.

In the revised guideline by ATA in 2009, they recommended a much more risk-orientated approach and suggested that "prophylactic central compartment lymph node dissection may be performed, especially in patients with advanced primary tumors" and "total thyroidectomy without prophylactic central compartment lymph node dissection may be appropriated for small (T1 or T2), non-invasive, clinically node negative patients.(27)

According to the revised ATA guideline, either unilateral or bilateral paratracheal LN would be regarded as a formal central compartment lymph node dissection but either would still result in morbidity in inexperienced hands. Other studies have shown that compared with unilateral (ipsilateral) prophylactic central compartment lymph node dissection, bilateral prophylactic central compartment lymph node dissection was associated with higher rate of temporary hypoparathyroidism (20.5% versus 48.0%; $P=0.009$), (26.8% versus 48.3%; $P=0.021$), while no significant difference in rate of postablation athyroglobulinemia (64% versus 57.1%, $P>0.05$) or recurrence (7.1% versus 8.6%, $P>0.05$).(28,29)

Although this study did not analyze, Kai-Pun Wong et al. recommend that if one has decided on performing a prophylactic central compartment lymph node dissection, an unilateral rather than a bilateral prophylactic central compartment lymph node dissection would appear to be the correct choice as it provides a balance between achieving surgical completeness and avoiding significant surgical morbidity.(30)

Currently, there are no prospective, randomized studies about the influence of central compartment lymph node dissection on the recurrence and prognosis of papillary thyroid cancer. The limitations of this study is that the number of subjects is relatively small, and the period the operation took place was different for the patient groups with only total thyroidectomy and with additional prophylactic central compartment lymph node dissection. From this, there were differences in the duration of follow-up observation, and about 52 months of a monitoring period is short for follow-up monitoring of papillary thyroid cancer. However, despite these limitations, the results of our research show that central neck lymph node dissection does not significantly increase post-operative complications and significantly lower the frequency of recurrences after surgery, especially local recurrence that de-

velops as central compartment lymph node metastasis.

CONCLUSION

Prophylactic central compartment lymph node dissection significantly lowered local recurrence, especially recurrence in the central compartment lymph node. However, recurrence in patients who did not receive prophylactic central compartment lymph node dissection usually occurred in the central compartment lymph nodes. The size of the lymph node metastasis were relatively small, and long-term follow up monitoring was limited regarding this so clinical meaning needs to be clarified in future research.

The results of this study show that prophylactic central compartment lymph node dissection in the treatment of papillary thyroid cancer was a good way to extend disease free survival while not significantly increasing the occurrence of postoperative complications.

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