Original Article

Evaluating the morbidity and efficacy of reoperative surgery in the central compartment for persistent / recurrent papillary thyroid carcinoma

Running head: Reoperative CND has low morbidity but also efficacy

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ABSTRACT

Background:

Although reoperative surgery in the central compartment (RCND) is indicated in bulky or progressive persistent/recurrent papillary thyroid carcinoma (PTC), its associated morbidity and disease outcomes remain unclear. We aimed to evaluate these by comparing them with patients who underwent primary central neck dissection (CND).

Methods:

After matching for age, sex, tumor size and initial tumor stage, the morbidity and outcomes of 50 consecutive patients who underwent RCND were compared with 75 patients who underwent primary therapeutic CND during the same period. Matching was performed blind to the morbidity and disease outcome of each patient. A stimulated thyroglobulin (sTg) < 2ng/mL was considered undetectable.

Results:

Relative to primary CND, the incidence of extranodal extension (p=0.010) and size of metastatic lymph nodes (p<0.001) were significantly greater in the RCND group. Postoperative hypoparathyroidism and vocal cord palsy rates were comparable in the two groups but there were two esophageal injuries in the RCND group and none in the primary CND group. The secondary CND group achieved significantly lower undetectable post-ablation sTg rate (12.0% vs. 52.0%,p=0.001) and worse 10-year disease-free survival (35.6% vs. 91.8%, p=0.001) and cancer-specific survival (82.0% vs. 98.5%, p=0.001) than the primary CND group.

Conclusions:

Although RCND for persistent / recurrent PTC could be performed with comparable morbidity to primary CND, it was associated with some serious complications. The short and long-term disease control appeared moderate with approximately one-tenth having undetectable sTg level 6-month after ablation and one-third remaining clinically disease-free after 10 years

Key words: papillary thyroid carcinoma; thyroidectomy; reoperation; central neck dissection; recurrent laryngeal nerve; postoperative hypoparathyroidism

INTRODUCTION

Papillary thyroid carcinoma (PTC) is the most common type of thyroid carcinoma and the age-adjusted incidence has doubled in the last 25 years.[1,2] Despite its good prognosis with 10-year cancer-specific survival (CSS) above 90%, locoregional recurrence is relatively common.[3] Local recurrences are found in 5-20% of patients with PTC, of which two thirds are localized in the cervical lymph nodes.[3] With the availability of ultrasensitive thyroglobulin (Tg) assays and high resolution ultrasonography (USG), the identification of asymptomatic, small-volume metastatic cervical lymph nodes has become relatively common.[4,5] Despite this, the benefit of surgically removing these small nodes remains unclear.[4] In fact, the revised American Thyroid Association recommends only surgical removal of clinically significant (i.e. size > 8mm in diameter) metastatic lymph nodes or recurrent disease to prevent future locoregional complications.[4] However, unlike the lateral compartment, untreated persistent / recurrent disease in the central compartment is associated with a significant higher risk of long-term morbidity, including loss or change in voice quality and swallowing because of the proximity of the recurrent laryngeal nerve (RLN) and the aerodigastic tract.[6-8] Furthermore, it increases the risk of cancer-specific deaths.[6-8] Therefore, reoperative surgery in the central compartment (RCND) is usually indicated.

Although most studies have reported relatively acceptable morbidity with some reporting rates similar to primary CND, morbidity does vary between studies and is subjected to publication bias.[6,9-15] Furthermore, the efficacy of RCND in disease control remains relatively unclear as not all studies have explicitly analyzed this outcome, particularly in terms of postoperative thyroglobulin levels and survivals.[5] As a result, our study aimed to review our experience in RCND specifically evaluating the surgical morbidity and efficacy in disease control.

PATIENTS AND METHODS

Patients

From 1992 to 2011, 1586 patients underwent surgery for histologically-proven PTC. Of these, 50 (3.2%) patients underwent RCND for persistent / recurrent PTC. We defined RCND as a comprehensive bilateral central lymph node dissection in a previously dissected central compartment. Patients who had initial thyroidectomy without CND were included. We also included those who developed recurrent tumor in the thyroid remnant and those with previously non-enlarged metastatic central neck lymph nodes or central neck lymph nodes which were not completely removed in the initial operation. However, patients who underwent re-excision of a normal / non-tumorous thyroid remnant or excision of lymph nodes only (i.e. "berry-picking") in a previously operated central compartment were not included. For patients who underwent ≥1 RCND, for simplicity, only the earliest reoperation was analyzed. To have a more meaningful comparison of surgical morbidity and disease outcomes of RCND, these 50 patients who had RCND were compared according to a 1.5:1 match with patients undergoing a therapeutic primary CND during the same period (i.e. those who underwent CND at the time of thyroidectomy). Over this period, there were 159 patients who had undergone a therapeutic primary CND. Those who underwent prophylactic CND were not included. The two groups were matched according to the following criteria: sex, age, tumor size and initial tumor stage. Matching was performed blind to the morbidity and disease outcome of each patient. Primary CND consisted of bilateral removal of clinically-involved central lymph nodes (cN1) at the time of the initial total thyroidectomy (TT).

Indications and technique for RCND

Persistent / recurrent disease was diagnosed using a combination of clinical evidence, USG, fine needle aspiration (FNA), post-radioiodine (RAI) scan, computed tomography (CT), magnetic resonance imaging (MRI) and /or FDG-PET/CT scan. In general, for patients with bulky (>8-10mm) and / or progressive central disease, RCND was preferred whereas for those with non-bulky (<5-8mm) and non-progressive central disease, close observation by regular USG was preferred.

In terms of surgical technique, the incision was generally made along the previous thyroidectomy incision. If required, the incision was extended laterally. A subplatysmal flap was elevated superiorly and inferiorly elevating the neck flaps. The inferior neck flap was usually elevated well below the sternal notch for easier retraction. To have a better surgical exposure, the upper part of the strap muscles on the side of reoperation was divided. For all cases, the RLN was identified first and traced along its course before proceeding to CND. In a densely scarred field, the intraoperative nerve stimulator probe was sometimes used for mapping out the course of the RLN.[16] Gentle dissection of the RLN was taken to dissect it from the central neck lymph nodes. The rest of the procedure was performed similar to a primary CND which had been described previously.[17]

Treatment protocol

Details of the treatment and follow-up protocols had been described previously.[18] Two months after surgery, a standard ablative RAI dose of 3 giga-Becquerels (GBq) or 80 millicuries (mCi) was given after LT4 withdrawal or with recombinant TSH (rTSH). TSH-suppressive LT4 treatment was commenced immediately afterwards. External beam radiotherapy (ERT) to the neck was given to patients with extensive extrathyroidal tumor extension, incomplete resection,

and/or extracapsular lymph node metastasis (40 Gy over 3 weeks for adjuvant treatment and 50 Gy over 4 weeks for gross residual disease). All treatment decisions were made at a multi-disciplinary meeting.

Complications

Both vocal cords were examined preoperatively and within 1 week of surgery. Any reduced cord movement was recorded as vocal cord palsy. Those with palsy were examined every 6-8 weeks by otolaryngologists in the first 6 months. The presence of palsy lasting > 6 months was regarded as permanent. To calculate vocal cord palsy rates, the number of nerves at risk was used as denominator. Calcium +/- calcitriol supplements were given selectively. For hypoparathyroidism, those taking calcium +/- calcitriol supplements were slowly weaned off their supplements. By definition, those who discontinued all supplements in the presence of normocalcemia ≤ 6 months after surgery were regarded as temporary hypoparathyroidism whereas those who continued for >6 months were categorized as permanent hypoparathyroidism.

Surveillance

All data including disease status and cause of death were prospectively collected after 1995. Follow-up visit was conducted at 3-monthly interval in the first 2 years, 6 monthly for the subsequent 3 years and annually thereafter. In addition to clinical examination, USG neck and Tg levels were performed at each follow-up. All Tg levels were measured in the same laboratory using the same immunometric assay. The assay used was the Immulite 2000 (Diagnostic Products Corp. Roche, Los Angeles, CA). This was calibrated against the CRM- 457 standard. A stimulated Tg (sTg) < 2.0ug/L was considered undetectable. Normal reference range was <0.5 –

55 ug/L and sensitivity was <0.2 ug/L. Clinical recurrences were diagnosed by USG, CT/ MRI or FDG-PET scan and confirmed by FNAC. Survival data including the cause of death were retrieved from the territory-wide computerized medical system and from death certificates or postmortem examinations.

Statistical analysis

Statistical analysis was performed by chi-square or Fisher's Exact test to compare categorical variables, and Mann-Whitney U test was used to compare continuous variables between groups. Continuous variables were expressed as medians with ranges. In the RCND group, survival and duration of follow-up were calculated from the time of RCND to the date of last follow-up or death while in the primary CND group, it was taken from the time of primary CND. Disease-free survival (DFS) and CSS were calculated by the Kaplan-Meier method. Survival outcomes were compared using the log-rank test. All statistical analyses were performed using SPSS version 18.0 (SPSS, Inc., Chicago, IL, USA).

RESULTS

Table 1 shows the baseline characteristics of the 50 patients who underwent RCND. Thirty-four patients underwent initial operation at our institution whereas the other 16 patients had initial operation performed elsewhere. All patients received 3GBq RAI ablation after initial operation while only one (2.0%) patient received ERT following initial operation. All had imageable one-sided recurrence in the central compartment and of these, 7 (14.0%) patients had palpable central neck recurrence. The USG and FDG-PET/CT was the most common combination for disease staging before surgery. Two (4.0%) patients had evidence of distant metastases at the time of RCND. Of the 20 patients who had RCND only, 2 also underwent a mediastinal clearance via a sternotomy for bulky upper mediastinal disease. Of the 6 patients who had tumor remnant excision, 4 patients had tumor remnant excision and CND while 2 patients had tumor remnant excision, CND and lateral selective neck dissection. Two patients in this tumor remnant excision subgroup also required tumor shaving from the trachea. The common sites for persistent / recurrent disease were adjacent to the RLN (38.0%), followed by paratracheal (34.0%) and para-esophageal (14.0%). Of the 20 (i.e. 12+8) patients who underwent CND at the initial operation and developed subsequent detectable recurrence on one side, 6 (30.0%) patients had microscopic or occult positive nodes on the other side.

Table 2 shows a comparison of clinicopathologic factors between those who underwent primary CND and RCND. As expected, age, sex, tumor size and primary tumor stage were comparable between the two groups. In terms of pathologic findings, the median number of central lymph nodes (CLNs) retrieved (7 vs. 7, p=0.489), positive CLNs examined (3 vs. 4, p=0.095) and lymph node ratio (LNR) (52.3% vs. 57.2%, p=0.512) were similar between the two groups The incidence of incidental parathyroid gland on excised specimen was also similar between the two

groups (17.3% vs. 18.0%, p=0.936) but the presence of extra-nodal extension was significantly more frequent in the RCND than primary CND (36.0% vs. 14.7%, p=0.010). Also the median size of metastatic central lymph node in RCND was also significantly larger than primary CND (15mm vs. 12mm, p<0.001).

Table 3 shows a comparison of morbidity and disease outcomes between primary CND and RCND. The temporary hypoparathyroidism rate was comparable between the two groups (8.0% vs. 14.0%, p=0.383). After excluding the 8 patients already taking calcium supplements before surgery in the RCND group, the permanent hypoparathyroidism rate was similar between the two groups (1.3% vs. 0.0%, p=1.000). The number of nerves-at-risk in primary CND and RCND was 150 and 100, respectively. After excluding the 6 patients with preoperative unilateral vocal cord palsy (due to tumor invasion to RLN), both temporary and permanent vocal cord palsy rates were similar between the two groups. Apart from hypoparathyroidism and vocal cord palsy, 2 patients in the RCND group suffered cervical esophageal injury, one of which was recognized intra-operatively and was repaired while the other was only recognized 2 days after surgery and required reoperation. In retrospect, both patients had incomplete primary tumor excision at the initial operation and both tumors recurred and partially invaded into the esophageal wall. The total morbidity rate was similar between two groups (20.0% vs. 28.0%, p=0.210). There was no in-hospital mortality. Within the RCND group, the temporary hypoparathyroidism and vocal cord palsy rates were comparable between those who had previous TT and those who had previous TT and neck dissection (4/27 vs. 3/23, p=1.000 and 3/27 vs. 3/23, p=1.000, respectively).

All patients after secondary CND received RAI ablation and 3 patients received additional ERT. The rate of detectable sTg (i.e. sTg ≥ 2ng/mL) was significantly higher in the secondary CND group (p=0.001). Despite the shorter median duration of follow-up, the number of postoperative recurrences was significantly higher in the secondary than primary group (26.0% vs. 6.7%, p=0.008) and also tended more likely to undergo subsequent reoperation than primary CND group (12.0% vs. 2.7%,p=0.066). The number of central compartment recurrences was also significantly higher in the secondary than primary group (12.0% vs. 0.0%, p=0.011). Other sites of recurrence were similar between the two groups.

Figure 1 shows the DFS survival curves between those who underwent primary and secondary groups. The 5-year and 10-year DFS between patients who underwent primary and secondary CND were 91.8% and 91.8% vs. 71.2% and 35.6%, respectively, p=0.001. There were 8 patients who developed locoregional recurrence after RCND. By logistic regression, age at diagnosis (p=0.386), sex (p=0.577), primary tumor size (p=0.346), *TNM* staging (p=0.637), number of CLNs retrieved (p=0.707), number of positive CLNs retrieved (p=0.632), LNR (p=0.819), extra-nodal extension (p=0.512) and size of CLN (p=0.454) were not significant factors for locoregional recurrence after RCND.

Figure 2 shows the CSS curves between those who underwent primary and secondary groups. The 5-year and 10-year CSS between patients who underwent primary and secondary groups were 98.5%% and 98.5% vs. 88.3% and 82.0%, respectively, p=0.001.

DISCUSSION

Consistent to previous studies, our data suggested that in well-selected cases, the morbidity of RCND for persistent / recurrent PTC was comparable to that of primary CND.[9,10] Table 4 shows a comparison of rate of complications, sTg and locoregional recurrence between our study and others. After excluding patients with preexisting hypoparathyroidism or vocal cord palsy before RCND, the temporary and permanent rates of these complications were similar between the two groups. However, it is worth noting that two (4.0%) patients in the RCND group did suffer iatrogenic injury to the cervical esophagus. Although one injury was recognized and repaired intraoperatively without any sequels, the other injury was missed and only recognized 2 days after surgery. That patient later developed an esophago-cutaneous fistula requiring a prolonged period of hospital stay. In retrospect, these two injuries were probably a direct result of the tumor invading into part of the esophagus. Therefore, in our opinion, although serious complications such as esophageal injury could result after RCND, the total morbidity of RCND appeared relatively acceptable and comparable to primary CND (28.0% vs. 20.0%, p=0.210). Nevertheless, the decision for RCND should not be taken lightly and should be based on weighing the risks and benefits of surgical reoperation with the risk of disease.

The other aspect which our study evaluated was disease control after RCND and that was assessed both biochemically and clinically. Using sTg <2ng/mL as biochemical undetectable disease, the RCND group achieved a significantly lower rate of undetectable post-ablation sTg than primary CND group (12.0% vs. 52.0%, p<0.001). This was despite both groups were matched for sex, age, tumor size and initial tumor stage. However, this finding was not entirely unexpected because the surgical indication between the two groups was quite different. For the

RCND group, approximately half were performed due to the bulkiness of the disease and the other half were due to disease progression whereas primary CND was usually done when there was clinical evidence of central lymph node metastasis (i.e. cN1) at the time of the initial TT. As a result, the RCND group had more advanced nodal disease as reflected by the greater incidence of extra-nodal extension (36.0% vs. 14.7%, p=0.010) and the size of metastatic central lymph nodes (17mm vs. 12mm, p<0.001) than primary CND group. Similarly, the incidence of preoperative unilateral vocal cord palsy in the RCND group was higher than that of the primary CND group (14.0% vs. 0.0%).

Apart from the undetectable post-ablation sTg, the overall recurrence rate in the RCND group was also significantly higher than the primary CND group (26.0% vs. 6.7%, p=0.008). Although it might appear high, they were relatively comparable to other similar series.[6,8,10,15] Of the 13 clinically detectable recurrences in the RCND group, 8 (61.5%) occurred either in the central or central and lateral compartments. In contrast, of the 5 clinical recurrences in the primary CND group, only one (20.0%) occurred in the central compartment. This implied the fact that despite performing a fairly comprehensive RCND, the disease control in the central compartment remained relatively moderate. It is also worth noting that of the 13 clinical recurrences, 5 (38.5%) (excluding the 2 patients with distant metastases before reoperation) developed distant disease. In fact, both 10-year DFS and CSS were significantly worse in the RCND group than the primary group (35.6% vs. 91.8%, p=0.001 and 82.0% vs. 98.5%, p=0.001). These findings underlined the importance of administrating adjuvant treatment after RCND as this group not only tended to recur locally but also in distant sites.

Despite these findings, our results should be interpreted cautiously because firstly, the surgical indication and selection for primary and RCND were very different (i.e. selection bias). For example, primary CND was done simply as part of the initial operation whereas the reason for RCND was to "prevent" future morbidities because of the bulkiness or progression of the central disease. We would also like to acknowledge that the RCND group was rather heterogeneous in terms of patients receiving different extent of initial operation prior to reoperation and different extent of persistent/recurrent disease. There were some patients who only had TT without CND while others had TT with CND as initial procedure. Ideally, these patients should have been separately analyzed but since the number of patients was few, we did not further perform subgroup analyses. Nevertheless, based on our data, the temporary hypoparathyroidism and vocal cord palsy rates appeared similar between the two subgroups. Also since this was a retrospective study, selection biases could not be completely ruled out.

Despite our findings, since RCND remains the only effective treatment in bulky and progressive central disease to prevent complications, the indication for RCND should remain unchanged despite the relatively poor long-term disease control. It remains unclear if performing RCND at an earlier stage (i.e. before disease becoming > 8-10mm or progressive) would significantly reduce the morbidity and improve the long-term disease outcomes.

CONCLUSIONS

Overall, in well selected cases, RCND for persistent / recurrent PTC could be performed with comparable morbidity to that of primary CND. However, it may be associated with some serious complications depending on the finding of the initial operation. In terms of disease control after RCND, only approximately one-tenth had undetectable post-ablation sTg level at 6 months after

surgery and one-third were clinically disease-free after 10 years.

REFERENECES

1. Cancer incidence and mortality in Hong Kong 1983-2010. Hong Kong Cancer Registry, Hong Kong. Available: http://www3.ha.org.hk/cancereg/ [Accessed on 15th January 2013]

2. SEER Cancer Statistics Review, 1975–2008. National Cancer Institute Surveillance Epidemiology and End Results [online], http://seer.cancer.gov/csr/1975_2008/ (2011).

3. Wong H, Wong KP, Yau T, Tang V, Leung R, Chiu J, Lang BH. (2012) Is there a role for unstimulated thyroglobulin velocity in predicting recurrence in papillary thyroid carcinoma patients with detectable thyroglobulin after radioiodine ablation? Ann Surg Oncol 19(11):3479-85.

4. Cooper DS, Doherty GM, Hauger BR et al. (2009) Revised American Thyroid Association management guidelines for patients with thyroid nodules and differentiated thyroid cancer. Thyroid 19:1167-214

5. Steward DL. (2012) Update in utility of secondary node dissection for papillary thyroid cancer. J Clin Endocrinol Metab. 97(10):3393-8.

6. Clayman GL, Agarwal G, Edeiken BS et al. (2011) Long-term outcome of comprehensive central compartment dissection in patients with recurrent/persistent papillary thyroid carcinoma. Thyroid. 21(12):1309-16.

7. Farrag TY, Agrawal N, Sheth S et al. (2007) Algorithm for safe and effective reoperative thyroid bed surgery for recurrent/persistent papillary thyroid carcinoma. Head Neck. 29(12):1069-74

8. Ito Y, Higashiyama T, Takamura Y et al. (2011) Prognosis of patients with papillary thyroid carcinoma showing postoperative recurrence to the central neck. World J Surg. 35(4):767-72.

9. Alvarado R, Sywak MS, Delbridge L, Sidhu SB. (2009) Central lymph node dissection as a secondary procedure for papillary thyroid cancer: Is there added morbidity? Surgery. 145(5):514-8.

10. Shen WT, Ogawa L, Ruan D et al. (2010) Central neck lymph node dissection for papillary thyroid cancer: comparison of complication and recurrence rates in 295 initial dissections and reoperations. Arch Surg. 145(3):272-5.

11. Kim MK, Mandel SH, Baloch Z et al. (2004) Morbidity following central compartment reoperation for recurrent or persistent thyroid cancer. Arch Otolaryngol Head Neck Surg. 130(10):1214-6.

12. Roh JL, Kim JM, Park CI. (2011) Central compartment reoperation for recurrent/persistent differentiated thyroid cancer: patterns of recurrence, morbidity, and prediction of postoperative hypocalcemia. Ann Surg Oncol. 18(5):1312-8

13. Ondik MP, Dezfoli S, Lipinski L, Ruggiero F, Goldenberg D. (2009) Secondary central compartment surgery for thyroid cancer. Laryngoscope. 119(10):1947-50

14. Al-Saif O, Farrar WB, Bloomston M et al. (2010) Long-term efficacy of lymph node reoperation for persistent papillary thyroid cancer. J Clin Endocrinol Metab. 95(5):2187-94.

15. Shah MD, Harris LD, Nassif RG et al. (2012) Efficacy and safety of central compartment neck dissection for recurrent thyroid carcinoma. Arch Otolaryngol Head Neck Surg. 138(1):33-7.

16. Chan WF, Lang BH, Lo CY. The role of intraoperative neuromonitoring of recurrent laryngeal nerve during thyroidectomy: a comparative study on 1000 nerves at risk. Surgery. 2006;140(6):866-72; discussion 872-3.

17. Lang BH, Wong KP, Wan KY, Lo CY. (2012) Impact of routine unilateral central neck dissection on preablative and postablative stimulated thyroglobulin levels after total thyroidectomy in papillary thyroid carcinoma. Ann Surg Oncol. 19(1):60-7.

18. Lang BH, Chow SM, Lo CY, Law SC, Lam KY.(2007) Staging systems for papillary thyroid carcinoma: a study of 2 tertiary referral centers. Ann Surg. 246(1):114-21

19. Farrag TY, Agrawal N, Sheth S, Bettegowda C, Ewertz M, Kim M, Tufano RP.(2007) Algorithm for safe and effective reoperative thyroid bed surgery for recurrent/persistent papillary thyroid carcinoma. Head Neck. 29(12):1069-74.

Table 1. Baseline characteristics of the 50 patients who underwent reoperative surgery in central compartment (RCND)

Characteristics	**Median or number of patients**	**Range or %**
Age at RCND (years)	54.2	18.9 – 85.1
Sex		
- Male	15	30.0
- Female	35	70.0
Main surgical indication for RCND		
- Bulky disease	26	52.0
- Progressive	24	48.0
Type and extent of initial operation		
- TT	27	54.0
- TT + CND	12	24.0
- TT + CND + SND	8	16.0
- TT + SND	3	6.0
Initial primary TNM tumor stage		
- Stage I	14	28.0
- Stage II	8	16.0
- Stage III	28	56.0
- Stage IV	0	0.0
Time interval from initial operation to RCND (months)	36.4	12.7 – 363.0
Imaging before RCND		
- USG + FDG/PET	33	66.0
- USG + CT / MRI	8	16.0
- USG alone	9	18.0
Type and extent of RCND		
- Excision of tumor remnant# + neck dissection	6	12.0

- CND only*	20	40.0
- CND + SND	24	48.0
Site of persistent/recurrent disease		
- Pre-tracheal area	4	8.0
- Para-tracheal area	17	34.0
- Para-esophageal area	7	14.0
- Adjacent to the RLN	19	38.0
- Upper mediastinal area	3	6.0

Abbreviations: TT = total thyroidectomy; CND = central neck dissection; SND = selective lateral neck dissection; USG = ultrasonography; FDG-PET = 18F-fluorodeoxyglucose positron emission tomography; CT = computed tomography; MRI = magnetic resonance imaging; RLN = recurrent laryngeal nerve

two patients had tracheal shaving

*two patients required sternotomy and mediastinal clearance

Table 2. A comparison of clinicopathologic factors between primary central neck dissection (CND) and reoperative surgery in central compartment (RCND)

Variable	**Primary CND (n=75)**	**RCND (n=50)**	***p*-value**
Age at surgery (years)*	47.9 (7.3 – 84.4)	54.2 (18.9 – 85.1)	0.234
Sex*			0.484
- Male	17 (22.7)	15 (30.0)	
- Female	58 (77.3)	35 (70.0)	
Primary tumor size (mm)*	20 (2 – 85)	21 (3 – 67)	0.556
Initial primary *TNM* tumor stage*			0.972
- Stage I	23 (30.7)	14 (28.0)	
- Stage II	13 (17.3)	8 (16.0)	
- Stage III	39 (52.0)	28 (56.0)	
- Stage IV	0 (0.0)	0 (0.0)	
Concomitant SND			0.805
- Yes	41 (54.7)	26 (52.0)	
- No	34 (45.3)	24 (48.0)	
Pathologic findings			
- Number of CLNs retrieved	7 (3 – 26)	7 (3 – 18)	0.489
- Number of positive CLNs retrieved	3 (1 – 7)	4 (1 – 14)	0.095
- Lymph node ratio (%)	52.3 (12.5 – 100.0)	57.2 (14.3 – 100.0)	0.512

- Incidental parathyroid in specimen	13 (17.3)	9 (18.0)	0.936
- Presence of extranodal extension	11 (14.7)	18 (36.0)	**0.010**
- Size of metastatic CLN (mm)	12 (3 – 35)	15 (7 – 30)	**<0.001**
Radioiodine ablation	75 (100.0)	50 (100.0)	**-**
Postoperative ERT	2 (2.7)	6 (12.0)	0.115

Bold signifies $p<0.05$ (i.e. statistically significant)

*matching was performed blind to morbidity and disease outcome

Abbreviations: CND = central neck dissection; SND = selective lateral neck dissection; CLN = central lymph node; ERT = external beam radiotherapy

Table 3. A comparison of morbidity and disease outcomes between primary central neck dissection (CND) and reoperative surgery in central compartment (RCND)

	Primary CND (n=75)	**RCND (n=50)**	***p*-value**
Postoperative hypoparathyroidism			
- Temporary	6 (8.0)	7 (14.0)	0.383
- Permanent	1 (1.3)	0 (0.0)*	1.000
Vocal cord palsy+			
- Temporary	6 (4.0)	6 (6.0)	0.553
- Permanent	2 (1.3)	1 (1.0)#	0.570
Esophageal injury	0 (0.0)	2 (4.0)	0.172
Total morbidity^	15 (20.0)	14 (28.0)	0.210
Postoperative sTg level			
- After ablation (ng/mL)	1.9 (<0.2 – 154)	28.5 (<0.2 – 130)	**<0.001**
- <2 ng/mL	39 (52.0)	6 (12.0)	**0.001**
- ≥2 ng/mL	36 (48.0)	44 (88.0)	**0.001**
Follow-up time since CND	78.2 (14.3 – 360.1)	42.0 (15.1 – 160.7)	0.170
Number of clinical recurrences	5 (6.7)	13 (26.0)	**0.008**
- Central recurrence	0 (0.0)	6 (12.0)	**0.011**
- Central and lateral recurrences	1 (1.3)	2 (4.0)	0.570
- Lateral recurrence	2 (2.7)	0 (0.0)	0.510
- Distant +/- local recurrences	2 (2.7)	5 (10.0)	0.127

Needing subsequent reoperation	2 (2.7)	6 (12.0)	0.066
Disease status at last follow-up			**<0.001**
- Alive without disease	71 (94.7)	31 (72.0)	
- Alive with disease	2 (2.7)	15 (30.0)	
- Died	2 (2.7)	5 (10.0)	

Abbreviation: sTg = stimulated thyroglobulin

* after excluding 8 patients requiring calcium and/or calcitriol supplements before RCND

after excluding 6 patients with preoperative vocal cord palsy

+ percentages calculated from number of nerves at risk

^those with one or more complications were counted as one

Table 4. A comparison of vocal cord palsy (VCP), hypocalcemia (hypoCa), rate of detectable stimulated thyroglobulin (sTg) and locoregional recurrence (LRR) between the present study and other similar series in reoperative surgery of the central compartment (RCND)

First author (size of cohort)	Year of publication	Temporary VCP (%)	Permanent VCP (%)	Temporary hypoCa (%)	Permanent hypoCa (%)	Rate of detectable (≥2ng/mL) sTg after RCND (%)	LRR after RCND (%)
Kim[11] (n=20)	2004	0 (0.0)	0 (0.0)	3 (16.7)	1 (5.6)	-	1 (5.0)
Farrag[7] (n=33)	2007	7 (21.2)	0 (0.0)	2 (6.1)	0 (0.0)	6.1*	0 (0.0)
Alvarado[9] (n=23)	2009	1 (3.3)	0 (0.0)	2 (8.7)	0 (0.0)	-	-
Ondik[13] (n=44)	2009	1 (2.1)	3 (6.4)	5 (11.4)	4 (9.1)	-	-
Clayman[19] (n=63)	2009	1 (1.6)	0 (0.0)	12 (19.0)	3 (4.8)	-	-
Shen[10] (n=106)	2010	5 (4.7)	2 (1.9)	25 (23.6)	1 (0.9)	-	31 (29.2)
Roh[12] (n=45)	2011	4 (5.8)	1 (1.4)	19 (46.3)	2 (4.9)	-	1 (2.2)
Shah[15] (n=82)	2012	3 (2.3)	3 (2.3)	17 (20.7)	6 (7.3)	48.5	17 (20.7)
Present study (n=50)	-	6 (6.0)	1 (1.0)	7 (14.0)	0 (0.0)	88.0	8 (16.0)

Note: The rate of VCP was calculated based on number of nerves at risk and those with the involved recurrent laryngeal nerve requiring intentional resection were excluded. Also rate of hypoCa was calculated based on patients with normal preoperative parathyroid function.

*basal thyroglobulin

LEGENDS

Figure 1. The disease-free survival curves between those who underwent primary central neck dissection (primary CND) and reoperative surgery in the central compartment (RCND)

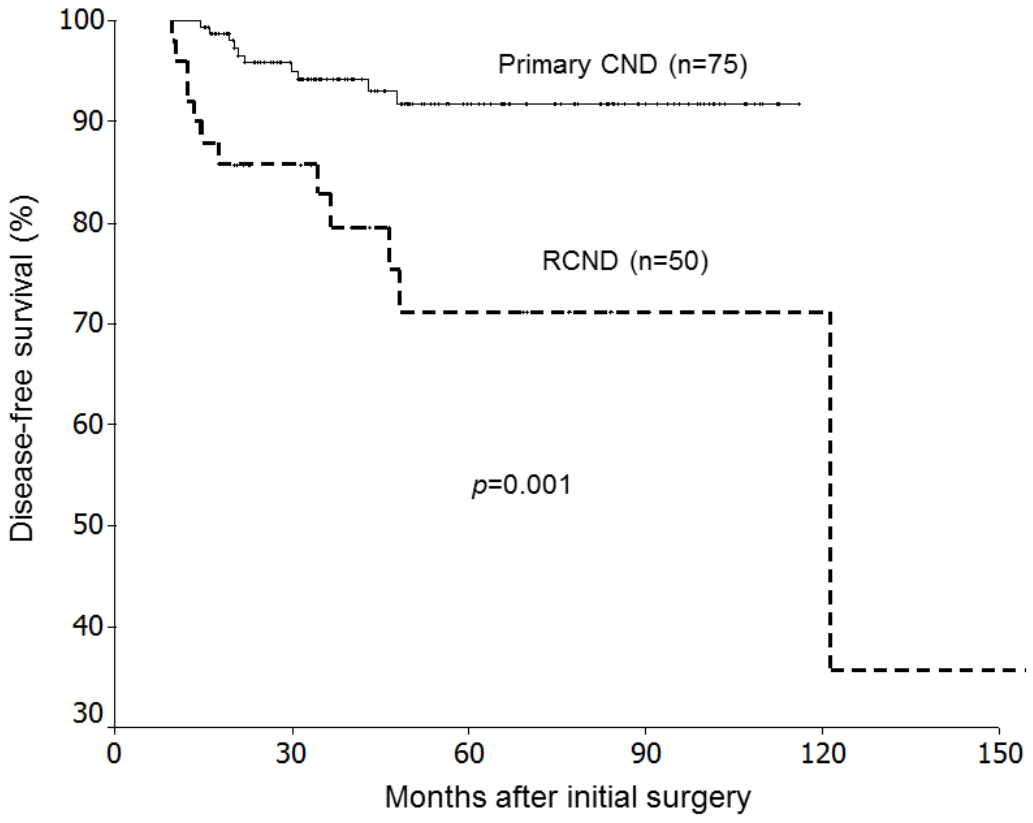

Figure 2. The cancer-specific survival curves between those who underwent primary central neck dissection (primary CND) and reoperative surgery in the central compartment (RCND).