Original Article

Thyroid lobectomy is sufficient for differentiated thyroid cancer with upgraded risk after surgery

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Background: It is difficult to reliably distinguish between American Thyroid Association (ATA) low-risk and intermediate-risk differentiated thyroid cancer (DTC) before surgery. Therefore, physicians are faced with a dilemma regarding the necessity and timing of completion total thyroidectomy (CT) after thyroid lobectomy (TL). We evaluated proper surgical methods by analyzing oncologic outcomes of TL in patients with DTC whose risk had been upgraded after surgery.

Methods: We retrospectively reviewed the medical records of 1,702 patients with DTC who underwent TL and ipsilateral central lymph node (LN) dissection between January 2006 and December 2011. The patients were classified into Group A (n=1,159; low risk; ≤5 central LN metastases or the absence of pathologic microscopic capsular invasion) and Group B (n=543; upgraded intermediate risk after surgery; >5 central LN metastases or the presence of pathologic microscopic capsular invasion). We analyzed their clinicopathological characteristics and recurrence-free survival.

Results: All 32 patients who experienced recurrence underwent CT. After the first operation, the duration until reoperation in Groups A and B were 8.00±2.74 (range, 3.42–12.17) and 5.10±3.09 (range, 1.25–11.67) years, respectively. There was no significant difference in recurrence rates, disease-related mortality rates, or 10-year recurrence-free survival rates between the two groups. The mean follow-up durations in Groups A and B were 10.22±1.58 and 10.13±1.47 years, respectively. Univariate analysis showed that sex, age, tumor size, multifocality, extrathyroidal extension (ETE), and number of central LN metastases were not associated with recurrence after TL, although the rate of central LN metastases was. Multivariate analysis showed that sex, age, tumor size, multifocality, ETE, central LN metastases, and the number of central LN metastases were not associated with recurrence after TL, although multifocality was.

Conclusions: TL with prophylactic central compartment neck dissection (CCND) is sufficient for patients with DTC whose risk is upgraded after surgery because they have a good prognosis at long-term follow-up. Larger-scale randomized clinical trials are required to confirm our findings.

Keywords: Thyroid lobectomy (TL); recurrence; prognosis; thyroid cancer

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Introduction

Thyroid cancer is the most common endocrine cancer, and its prevalence has gradually increased (1-4). Differentiated thyroid cancers (DTCs), including papillary thyroid cancer (PTC) and follicular thyroid cancer (FTC), show a relatively good prognosis when appropriate treatments are administered, and many studies have been performed on the extent of thyroidectomy (5-9).

Complications occur in 0.5% to 20% of patients who undergo completion total thyroidectomy (CT) after thyroid lobectomy (TL), and patients who undergo CT must receive thyroid hormones for the rest of their lives. Therefore, candidates for CT should be carefully selected (10-13). The 2015 American Thyroid Association (ATA) guidelines recommend CT for patients with an unclear diagnosis after lobectomy, complete resection of multicentric disease, and efficient radioactive iodine (RAI) therapy. In addition, CT is recommended for patients categorized as high risk according to the ATA guidelines based on clinicopathologic results after TL (14).

The 2015 ATA guidelines classify gross extrathyroidal extension (ETE), lymph node (LN) metastasis, and distant metastasis as high-risk diseases, and they recommend initial total thyroidectomy (TT) in these cases. However, the necessity of CT after TL remains controversial in patients categorized as ATA intermediate risk, which is characterized by clinical N1 disease, >5 pathologic N1 LNs with all involved LNs <3 cm in the largest dimension, microscopic capsular invasion, vascular invasion, aggressive histology, or RAI-avid metastatic foci in the neck on the first post-treatment whole-body RAI scan. The recurrence rate in patients with ATA intermediate-risk DTC has been reported to range from 21% to 36%, and the ATA guidelines recommend that the decision to perform TL or TT in these patients should be based on the attending physician's judgment (14-16). Several studies have reported that it is difficult to reliably distinguish between ATA low-risk and ATA intermediate-risk DTC before surgery, as they are distinguished based on the final pathologic result (17-19). Therefore, physicians are faced with a dilemma regarding the necessity and timing of CT after TL because the indication for CT after TL is not clear in patients with DTC whose risk has been upgraded after surgery.

This retrospective study was designed to evaluate proper surgical methods by comparing the postoperative oncologic outcomes and long-term prognosis of patients with DTC whose risk had been upgraded after surgery at a single medical center. We present the following article in accordance with the STROBE reporting checklist (available at https://gs.amegroups.com/article/view/10.21037/gs-22-158/rc).

Methods

Patients

We retrospectively reviewed the medical records of 2,830 patients with DTC who underwent TL at Severance Hospital between January 2006 and December 2011. All patients' statuses were evaluated by preoperative ultrasonography and computed tomography. Since surgery was performed according to the 2009 ATA guideline during this period, patients with clinical LN metastasis underwent TT. Therefore, all LNs of enrolled patients were micrometastasis. Patients in whom gross ETE was observed or LNs were grossly enlarged during surgery, which resulted in conversion to TT, were excluded from this study. All patients underwent prophylactic ipsilateral central compartment neck dissection (CCND), including those of the pre-laryngeal, pre-tracheal, and paratracheal LNs. If the patient had recurrence in the contralateral lobe, we performed CT. Lateral neck dissection was performed when there was a recurrence at the lateral neck. We considered the case of no outpatient visit within 2 years as follow-up loss. A total of 1,128 of the 2,830 patients were lost to follow-up, and the remaining 1,702 patients were included in the analyses. Microscopic capsular invasion was defined as findings of capsular invasion confirmed through microscopic examination in the final pathology report. Multifocality was defined as the presence of two or more cancer foci in the same lobe. Recurrence was defined as a newly discovered lesion on ultrasonography that was confirmed as cancer through fine-needle aspiration biopsy during the postoperative follow-up period.

The patients were divided into two groups according to number of metastatic LNs, and microscopic capsular invasion in the final pathology report. Group A [1,159 patients (68.1%), low risk] comprised patients with ≤5 central LN metastases, or no pathologic microscopic capsular invasion. Group B [543 patients (31.9%), upgraded intermediate risk after surgery] comprised patients with >5 central LN metastases, or pathologic microscopic capsular invasion.

Group A was further divided into two subgroups for subgroup analyses. Group A-1 (963 patients, 56.6%) comprised patients with no central LN metastasis, and

Group A-2 (196 patients, 11.5%) comprised patients with 1–5 central LN metastases. We then analyzed the characteristics and recurrence rates among the three groups (Group A-1, Group A-2, and Group B).

Statistical analysis

Statistical analyses were performed using SPSS statistical software (version 27.0; IBM Corp., Armonk, NY, USA). Fisher's exact test and Pearson's chi-square test were used to compare categorical variables. Continuous variables were compared using Student's *t*-test. A multivariate Cox proportional hazards regression model was used to evaluate the variables associated with a risk of recurrence. Recurrence-free survival (RFS) curves were constructed using the Kaplan-Meier method and compared using the log-rank test. Post-hoc analyses were constructed, and adjusted P values were calculated using the Bonferroni correction, Scheffe's test, and Dunnett T3 test.

Ethical approval

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Institutional Ethics Committee of Severance Hospital (No. 4-2021-0614), and obtaining individual consent for this retrospective analysis was waived.

Results

Clinicopathologic characteristics of enrolled patients and those lost to follow-up

There were no differences in sex, age, tumor size, cancer subtype, microscopic capsular invasion, multifocality, and the number of central LN metastases between enrolled patients and those lost to follow-up, although there was a difference in the recurrence rate (1.9% *vs.* 0.5%, P=0.002). The mean duration of follow-up of enrolled patients was longer than that of patients lost to follow-up (10.19±1.54 *vs.* 5.35±2.69 years, P<0.001) (*Table 1*).

Clinicopathologic characteristics of Groups A and B

Compared with Group A, Group B had a larger tumor size (0.54±0.46 *vs.* 0.68±0.53 cm, P<0.001), higher rate of central LN metastases (27.1% *vs.* 16.9%, P<0.001), and greater number of central LN metastases (0.34±0.86 *vs.* 0.72±1.52, P<0.001). There was no significant difference between the two groups in recurrence rates (1.6% *vs.* 2.4%, P=0.285). The mean follow-up durations in Groups A and B were 10.22±1.58 and 10.13±1.47 years, respectively (P=0.287). Nineteen patients had FTC (six in Group A and thirteen in Group B), and six patients had Hurthle cell cancer (HCC) (three in Group A and three in Group B); however, they did not experience recurrence. There were three patients with diffuse sclerosing PTC in Group B, while the PTCs of the other two groups were the conventional type. There was no difference in disease-related mortality between the two groups (*Table 2*).

Recurrence in Groups A and B

All 32 patients who experienced recurrence underwent CT. After the first operation, the duration until reoperation with CT was 8.00±2.74 years for Group A (range, 3.42–12.17 years) and 5.10±3.09 years for B (range, 1.25–11.67 years). Of these, 8 patients underwent lateral neck dissection (four in Group A and four in Group B) and 13 underwent RAI (seven in Group A and six in Group B). One 25-year-old woman in Group A initially underwent left TL and had recurrence in the contralateral lobe 8 years later. She underwent CT and RAI, but recurrence of the right lateral neck occurred after 4 years. Finally, she underwent right lateral neck dissection and second RAI. The 10-year RFS rates of Groups A and B were 98.8% and 98.2%, respectively, and this difference was not significant (P=0.162) (*Figure 1*).

Univariate analysis showed that sex, age, tumor size, multifocality, microscopic capsular invasion, and the number of central LN metastases were not associated with recurrence after TL; however, central LN metastasis was associated with recurrence [hazard ratio (HR) =2.257; 95% CI: 1.047–4.865). Multivariate analysis showed that sex, age, tumor size, microscopic capsular invasion, central LN metastasis, and number of central LN metastases were not associated with recurrence after TL; however, multifocality was associated with recurrence (HR =2.775; 95% CI: 1.153–6.677) (*Table 3*).

Clinicopathologic characteristics of Groups A-1, A-2, and B

There were differences in sex, tumor size, cancer subtype, microscopic capsular invasion, multifocality, number of retrieved central LNs, and number of central LN metastases among the three groups. However, there were no significant differences among the three groups in recurrence rate (1.5%

Table 1 Clinicopathologic characteristics of patients who were enrolled and those lost to follow-up group

Variable	Enrolled (n=1,702)	Lost to follow-up (n=1,128)	P value
Sex, n (%)			0.812
Male	248 (14.6)	168 (14.9)	
Female	1,454 (85.4)	960 (85.1)	
Age, years (%, mean ± SD)			0.051
<55	1,453 (85.4, 40.5±8.0)	932 (82.6, 39.6±8.0)	
≥55	249 (14.6, 59.9±4.4)	196 (17.4, 62.5±6.1)	
Tumor size, cm (mean ± SD, SEM)	0.59±0.49 (0.01)	0.59±0.54 (0.02)	0.775
Cancer subtype, n (%)			0.934
Papillary thyroid cancer	1,677 (98.5)	1,108 (98.2)	
Follicular thyroid cancer	19 (1.1)	19 (1.7)	
Hurthle cell cancer	6 (0.4)	1 (0.1)	
Microscopic capsular invasion, n (%)	535 (31.4)	351 (31.1)	0.859
Multifocality, n (%)	178 (10.5)	113 (10.0)	0.706
Central lymph node metastasis, n (%)	344 (20.2)	237 (21.0)	0.606
Number of central lymph node (mean ± SD, SEM)			
Total	5.16±3.91 (0.10)	4.93±3.54 (0.11)	0.119
Positive	0.46±1.12 (0.02)	0.46±1.10 (0.03)	0.922
Recurrence, n (%)	32 (1.9)	6 (0.5)	0.002
Follow-up duration, years (mean ± SD, SEM)	10.19±1.54 (0.04)	5.35±2.69 (0.08)	<0.001

SEM, standard error of the mean.

vs. 2.6% *vs.* 2.4%, P=0.332) (*Table 4*).

Compared with Group A-1, Group A-2 had a significantly higher proportion of men (14.0% *vs.* 23.5%, P=0.001), more multifocality (9.0% *vs.* 14.8%, P=0.014), a higher number of retrieved central LNs (4.97±3.92 *vs.* 5.99±3.99, P=0.004), and more central LN metastases (0.0±0.0 *vs.* 1.80±1.14, P<0.001).

Compared with Group A-1, Group B had a larger tumor size (0.54±0.49 *vs.* 0.68±0.53 cm, P<0.001), a more aggressive cancer subtype (0.9% *vs.* 3.0%, P=0.010), and more central LN metastases (0.0±0.0 *vs.* 0.72±1.52, P<0.001).

Compared with Group A-2, Group B had a lower proportion of men (12.3% *vs.* 23.5%, P<0.001), larger tumor size (0.56±0.30 *vs.* 0.68±0.53 cm, P=0.017), a smaller number of retrieved central LNs (5.15±3.83 *vs.* 5.99±3.99, P=0.038), and fewer central LN metastases (1.80±1.14 *vs.* 0.72±1.52, P<0.001) (*Table 5*).

Recurrence in Groups A-1, A-2, and B

There was no significant difference between Groups A-1 and A-2 (98.9% *vs.* 98.3%, P=0.179), between Group A-1 and B (98.9% *vs.* 98.2%, P=0.095) and between Groups A-2 and B (98.3% *vs.* 98.2%, P=0.978) in the 10-year RFS rates (*Figure 2*).

Surgical complications in Groups A and B

The surgical complication rates in Groups A and B were 6.4% and 5.3%, respectively, and there was no significant difference between the two groups (P=0.400). In addition, there were no differences in the incidence rates of hematoma, seroma, transient hoarseness, chyle leakage, transient hypocalcemia, and injury of the recurrent laryngeal nerve between the two groups (*Table 6*).

Table 2 Clinicopathologic characteristics of patients in Group A and Group B

Variable	Group A (n=1,159)	Group B (n=543)	P value
Sex, n (%)			0.074
Male	181 (15.6)	67 (12.3)	
Female	978 (84.4)	476 (87.7)	
Age, years (%, mean ± SD)			0.600
<55	993 (85.7, 40.4±8.0)	460 (84.7, 40.6±8.1)	
≥55	166 (14.3, 60.2±4.6)	83 (15.3, 59.3±4.0)	
Tumor size, cm (mean ± SD, SEM)	0.54±0.46 (0.01)	0.68±0.53 (0.02)	<0.001
Cancer subtype, n (%)			0.003
Papillary thyroid cancer	1,150 (99.2)	527 (97.1)	
Follicular thyroid cancer	6 (0.5)	13 (2.4)	
Hurthle cell cancer	3 (0.3)	3 (0.5)	
Microscopic capsular invasion, n (%)	0	535 (98.5)	<0.001
Multifocality, n (%)	116 (10.0)	62 (11.4)	0.376
Central lymph node metastasis, n (%)	196 (16.9)	147 (27.1)	<0.001
Number of central lymph node (mean ± SD, SEM)			
Total	5.17±3.95 (0.12)	5.15±3.83 (0.17)	0.940
Positive	0.34±0.86 (0.02)	0.72±1.52 (0.07)	<0.001
Recurrence, n (%)	19 (1.6)	13 (2.4)	0.285
Follow-up duration, years (mean ± SD, SEM)	10.22±1.58 (0.05)	10.13±1.47 (0.06)	0.287

Group A: patients with ≤5 positive central lymph nodes and no pathologic microscopic capsular invasion. Group B: patients with >5 positive central lymph nodes, or pathologic microscopic capsular invasion. SEM, standard error of the mean.

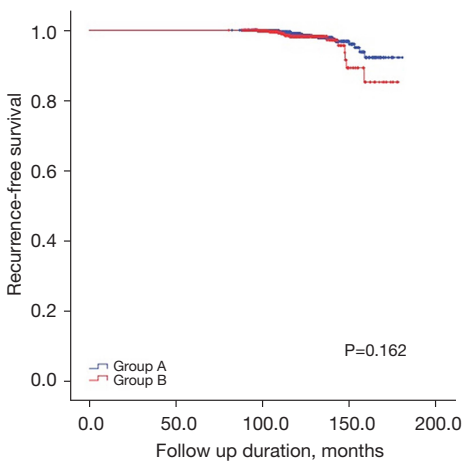

Figure 1 Kaplan-Meier curve of recurrence-free survival (P=0.162). Group A: patients with ≤5 positive central lymph nodes and no pathologic microscopic capsular invasion. Group B: patients with >5 positive central lymph nodes, or pathologic microscopic capsular invasion.

Discussion

Previous studies have reported the 10-year recurrence and mortality rates of DTC as 21–25% and 2–8%, respectively (20-22). Owing to the relatively good prognosis, surgical extension and treatment policies are continuously discussed to avoid unnecessary surgery and harm to the patient (23-27).

LN metastasis, one of the criteria for categorizing DTC as ATA intermediate risk, is very common in patients with DTC and is observed in up to 80% of cases (28,29). It remains controversial whether occult LN micrometastasis is associated with recurrence, although it is not associated with disease-specific mortality (30-32). Our study showed that LN micrometastasis was not associated with the recurrence rate. Furthermore, the number of metastatic LNs was not associated with the recurrence rate, and no patients died from DTC during the follow-up period.

Microscopic capsular invasion is found in 5% to 45% of

Table 3 Cox proportional hazard analysis of variables predicting recurrence after thyroid lobectomy

Variable	N	Recurrence (n, %)	Univariate analysis		Multivariate analysis	
			HR (95% CI)	P value	HR (95% CI)	P value
Sex				0.452		0.330
Male	248	6 (2.4)	1.000		1.000	
Female	1,454	26 (1.8)	0.734 (0.299–1.803)		0.631 (0.250–1.593)	
Age, years				0.612		0.242
<55	1,453	29 (2.0)	1.000		1.000	
≥55	249	3 (1.2)	0.599 (0.181–1.981)		0.422 (0.100–1.791)	
Tumor size, cm				0.189		0.982
<4	1,691	31 (1.8)	1.000		1.000	
≥4	11	1 (9.1)	5.355 (0.665–43.125)		0.000 (0.000–1.391)	
Multifocality				0.071		0.023
Absent	1,524	25 (1.6)	1.000		1.000	
Present	178	7 (3.9)	2.455 (1.046–5.759)		2.775 (1.153–6.677)	
Microscopic capsular invasion				0.258		0.151
Absent	1,167	19 (1.6)	1.000		1.000	
Present	535	13 (2.4)	1.505 (0.738–3.070)		1.749 (0.816–3.752)	
CLN metastasis				0.033		0.163
Absent	1,175	17 (1.4)	1.000		1.000	
Present	343	11 (3.2)	2.257 (1.047–4.865)		1.783 (0.791–4.020)	
Number of CLN metastasis				0.230		0.462
≤5	1,504	27 (1.8)	1.000		1.000	
>5	14	1 (7.1)	4.208 (0.531–33.323)		2.180 (0.273–17.428)	

HR, hazard ratio; CLN, central lymph node.

patients with DTC, and patients with DTC are classified as ATA low risk and intermediate risk depending on the presence or absence of microscopic capsular invasion (14,16). Several studies have reported that microscopic capsular invasion is not related to recurrence, and our results were consistent with this finding (33-35).

Multifocality was found to affect the recurrence rate in the multivariate analysis. Several studies have reported that multifocality was associated with a risk of PTC in the contralateral thyroid lobe, and the European Society of Endocrine Surgeons consensus statement recommends TT in cases of multifocality (36-38). However, the ATA guidelines do not consider the presence of multifocality in the decision to perform TT (14). Additionally, several studies demonstrated that multifocality was not an indication for CT (39,40). At our institution, multifocality is usually an incidental finding in the final pathology report. Since the recurrence rate was very low, we believe that TL is sufficient for patients with multifocal DTC.

FTC and HCC are known to have a relatively poorer prognosis than PTC (41-44). However, since no patients with FTC and HCC experienced recurrence in our study, the effect of cancer subtype on recurrence could not be analyzed. Because of the small number of such patients, further studies are needed in the future.

RAI therapy should be considered to prevent recurrence and improve disease-specific survival. Several studies have demonstrated that RAI therapy has no significant effect on recurrence and disease-specific survival in patients with low-risk DTC, but there is a significant effect in patients

Table 4 Clinicopathologic characteristics of patients in Group A-1, Group A-2, and Group B

Variable	Group A-1 (n=963)	Group A-2 (n=196)	Group B (n=543)	P value
Sex, n (%)				0.001
Male	135 (14.0)	46 (23.5)	67 (12.3)	
Female	828 (86.0)	150 (76.5)	476 (87.7)	
Age, years, n (%)				0.255
<55	818 (84.9)	175 (89.3)	460 (84.7)	
≥55	145 (15.1)	21 (10.7)	83 (15.3)	
Tumor size, cm (mean ± SD, SEM)	0.54±0.49 (0.02)	0.56±0.30 (0.02)	0.68±0.53 (0.02)	<0.001
Cancer subtype, n (%)				0.013
Papillary thyroid cancer	954 (99.1)	196 (100.0)	527 (97.1)	
Follicular thyroid cancer	6 (0.6)	0	13 (2.4)	
Hurthle cell cancer	3 (0.3)	0	3 (0.6)	
Microscopic capsular invasion, n (%)	0	0	535 (98.5)	<0.001
Multifocality, n (%)	87 (9.0)	29 (14.8)	62 (11.4)	0.038
Central lymph node metastasis, n (%)	0	196 (100.0)	147 (30.6)	<0.001
Number of central lymph node (mean ± SD, SEM)				
Total	4.97±3.92 (0.14)	5.99±3.99 (0.29)	5.15±3.83 (0.18)	0.004
Positive	0.0±0.0	1.80±1.14 (0.08)	0.72±1.52 (0.07)	<0.001
Recurrence, n (%)	14 (1.5)	5 (2.6)	13 (2.4)	0.332
Follow-up duration, years (mean ± SD, SEM)	10.25±1.60 (0.05)	10.10±1.47 (0.10)	10.13±1.47 (0.06)	0.278

Group A-1: patients with no central lymph node metastasis and no pathologic microscopic capsular invasion. Group A-2: patients with 1–5 positive central lymph nodes and pathologic microscopic capsular invasion. Group B: patients with >5 positive central lymph nodes, or pathologic microscopic capsular invasion. SEM, standard error of the mean.

Table 5 Comparison of the P values from the post-hoc analysis among three groups

Variable	P		
	(Group A-1) *vs.* (Group A-2)	(Group A-1) *vs.* (Group B)	(Group A-2) *vs.* (Group B)
Sex*	0.001	0.358	<0.001
Age, years*	0.114	0.906	0.115
Tumor size, cm**	0.786	<0.001	0.017
Cancer subtype*	0.397	0.010	0.052
Microscopic capsular invasion*	N/A	<0.001	<0.001
Multifocality*	0.014	0.137	0.217
Central lymph node metastasis	<0.001	<0.001	<0.001
Number of central lymph node			
Total (retrieved) **	0.004	0.730	0.038
Positive**	<0.001	<0.001	<0.001
Recurrence*	0.348	0.187	1.000

Group A-1: patients with no central lymph node metastasis and no pathologic microscopic capsular invasion. Group A-2: patients with 1–5 positive central lymph nodes and no pathologic microscopic capsular invasion. Group B: patients with >5 positive central lymph nodes, or pathologic microscopic capsular invasion. *, P values calculated using the χ^2 test or Fisher's exact test (adjusted P value =0.016). **, P values calculated using the Scheffe test or the Dunnett T3 test.

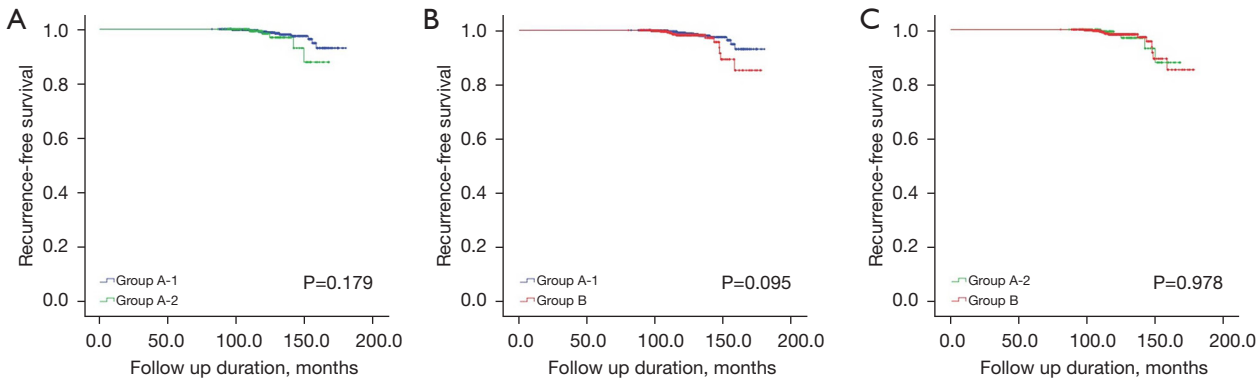

Figure 2 Kaplan-Meier curve of recurrence-free survival in the three groups. (A) Group A-1 and Group A-2 (P=0.179). (B) Group A-1 and Group B (P=0.095). (C) Group A-2 and Group B (P=0.978). Group A-1: patients with no central lymph node metastasis. Group A-2: patients with 1–5 positive central lymph nodes. Group B: patients with >5 positive central lymph nodes, or pathologic microscopic capsular invasion.

Table 6 Postoperative complications of Group A and Group B

Variable	Group A (n=1,159)	Group B (n=543)	P value
Complication, n (%)			0.400
Absent	1,085 (93.6)	514 (94.7)	
Present	74 (6.4)	29 (5.3)	
Hematoma, n (%)			0.657
Absent	1,156 (99.7)	541 (99.6)	
Present	3 (0.3)	2 (0.4)	
Seroma, n (%)			0.854
Absent	1,145 (98.8)	537 (98.9)	
Present	14 (1.2)	6 (1.1)	
Hoarseness (transient), n (%)			0.896
Absent	1,147 (99.0)	537 (98.9)	
Present	12 (1.0)	6 (1.1)	
Chyle leakage, n (%)			1.000
Absent	1,151 (99.3)	540 (99.4)	
Present	8 (0.7)	3 (0.6)	
Hypocalcemia (transient), n (%)			0.165
Absent	1,141 (98.4)	539 (99.3)	
Present	18 (1.6)	4 (0.7)	
RLN injury, n (%)			0.556
Absent	1,156 (99.7)	543 (100.0)	
Present	3 (0.3)	0	

Group A: patients with ≤5 positive central lymph nodes and no pathologic microscopic capsular invasion. Group B: patients with >5 positive central lymph nodes, or pathologic microscopic capsular invasion. RLN, recurrent laryngeal nerve.

with high-risk DTC (45-47). In line with these studies, the ATA guidelines do not recommend RAI therapy for patients with low-risk DTC but recommend it for patients with high-risk DTC.

Nonetheless, the effectiveness of RAI therapy in patients with intermediate-risk DTC remains controversial. Orosco *et al.* demonstrated that RAI therapy in patients with intermediate-risk DTC was not associated with disease-specific mortality (48). Wang *et al.* suggested that RAI therapy improves disease-specific survival in selected patients with intermediate-risk DTC (49). Due to differences in the results of several studies on RAI therapy and the lack of large-scale randomized clinical trials, there are no definitive guidelines for RAI therapy in patients with intermediate-risk DTC. Therefore, when the final pathology report after TL shows findings indicative of intermediate risk, physicians face the dilemma of whether to perform CT for RAI therapy.

Interestingly, the recurrence rate in patients with DTC whose risk had been upgraded after surgery (Group B) was very low (2.4%, 10-year RFS: 98.2%). Bosset *et al.* demonstrated that the recurrence rate of intermediate-risk PTC was higher than low-risk PTC in patients who underwent TL (28.6% *vs.* 7.1%) (50). However, they included aggressive histologic cancer types like poorly-differentiated cancer and diffuse sclerosing PTC. Additionally, there was no mention of central LN dissection, and they did not analyze central LN metastasis. We thought that this may have affected the recurrence rate. We considered this to be the result of R0 resection with sufficient prophylactic CCND. Since the average number of LNs retrieved through prophylactic CCND was reported to be 13±5, we considered that the LNs of our patients were sufficiently removed (21,51). In addition, although the incidence of complications after CT is relatively diverse (0.5% to 20%), these complications can be completely prevented by avoiding unnecessary surgery (10-12). Therefore, we believe that CT for RAI is not necessary in patients with DTC whose risk is upgraded after surgery if an experienced endocrine surgeon performs TL with prophylactic CCND.

The recurrence rate of Group B did not differ from that of Group A at long-term follow-up, and the recurrence rate was very low. In addition, there was no disease-specific mortality during this period. As this result was obtained in a sufficient number of enrolled patients over the follow-up period, we suggest that periodic surveillance without CT is sufficient for patients with DTC whose risk is upgraded after surgery.

Subgroup analysis was performed to compare the prognosis of patients with very low-risk DTC (Group A-1) and those with intermediate-risk DTC (Group B), and it revealed that the recurrence rate of patients with intermediate-risk DTC did not differ from that of those with very low-risk DTC. The only factor affecting recurrence was multifocality, and there was no difference between Groups A-1 and B. Although there were more patients with FTC in Group B than in Group A-1, the effect on recurrence could not be analyzed because there was no recurrence in patients with FTC. When we calculated the statistical power, it was 0.363. Assuming a power of 0.8 and significance level of 0.05, the required sample sizes were 2,918 and 1,646, respectively. Since the progression of DTC is slow and the recurrence rate is low, the 10-year follow-up duration of our study is rather short. To compensate for this, a larger number of patients or longer follow-up will be needed in the future.

Although the number of recurrence was too small for statistical analysis, the ratio of lateral neck dissection in Group B was higher than that of Group A (4/13, 30.8% *vs.* 4/19, 21.1%). Because several studies demonstrated that central LN metastasis was associated with lateral LN metastasis, we believe that this difference occurred from higher central LN metastasis of Group B (52-54). However, the recurrence rate of lateral neck was very low (8/1,702, 0.4%). Therefore, active and frequent follow-up was thought to be sufficient for patients with DTC whose risk is upgraded after surgery.

Criteria for classifying ATA intermediate-risk include the existence of vascular invasion and aggressive pathology type. However, we could not identify the presence of vascular invasion due to a lack of records. In addition, most of the PTCs were the conventional type and only a few of them were the diffuse sclerosing type; therefore, there were not enough numbers to analyze.

Although all preoperative clinical T3 and N1 patients had intermediate risk, these patients underwent TT and were excluded from this study. Therefore, the patients in Group B did not represent all ATA intermediate-risk but only those whose risk had been upgraded to intermediate-risk after surgery.

Considering all of the above, and since there was no significant difference in long-term prognosis between patients with low-risk DTC and those with DTC whose risk was upgraded after surgery, we suggest that TL with prophylactic CCND is sufficient for patients with DTC whose risk is upgraded after surgery. In addition, we

carefully recommend that strict surveillance without RAI after immediate CT is sufficient in these patients.

This study had some limitations. First, various biases may have occurred because this was a retrospective study. Multivariate analysis was performed to correct this, but large-scale randomized clinical trials will be needed to confirm our findings in the future. Second, recent studies have demonstrated that *BRAF*^{V600E} or *TERT* promoter mutations are associated with aggressive features and a poor prognosis in patients with thyroid cancer (55-58). However, the effects of these mutations on prognosis could not be analyzed in this study because of limited data. Additional research is needed in the future. Third, since DTC has a generally good prognosis, the 10-year follow-up duration is rather short. To address this, longer-term follow-up and analysis will be needed. Finally, there is a possibility of selection bias owing to the relatively large number of patients who were lost to follow-up (39.9%). However, there were no differences between the characteristics of the enrolled patients and those who were lost to follow up, and the effect of this factor on the outcome was considered negligible because the number of enrolled patients was sufficient. The recurrence rate of the enrolled patients was higher than that of those lost to follow up (1.9% *vs.* 0.5%, P=0.002); however, this might be due to the short follow-up period of the patients lost to follow up. Since the difference in recurrence rate between the two groups was not large, it did not affect the interpretation of the results.

Conclusions

In conclusion, TL with prophylactic CCND is sufficient for patients with DTC whose risk was upgraded after surgery, because they have a good prognosis at long-term follow-up. Larger-scale randomized clinical trials are required to confirm our findings.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://gs.amegroups.com/article/view/10.21037/gs-22-158/rc

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://gs.amegroups.com/article/view/10.21037/gs-22-158/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Institutional Ethics Committee of Severance Hospital (No. 4-2021-0614), and obtaining individual consent for this retrospective analysis was waived.

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