Endocrine

The impact of completion thyroidectomy followed by radioactive iodine ablation for patients with lymph node recurrence of papillary thyroid carcinoma

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ABSTRACT

Background: Although lobectomy is considered acceptable as a primary surgical treatment for papillary thyroid carcinoma in properly selected patients, a standard treatment for postlobectomy lymph node recurrence has not been established. Here we compared the effectiveness of therapy with lymphadenectomy alone to that of treatment with completion thyroidectomy and lymphadenectomy followed by radioactive iodine.

Methods: This was a retrospective study of patients with papillary thyroid carcinoma who underwent surgery for lymph node recurrence in the period from January 2003 to December 2008, all of whom had previously undergone initial lobectomy with or without lymph node dissection. One-hundred and twenty-five patients were included in the primary analysis.

Results: Ninety-eight of these patients underwent lymphadenectomy alone (L group), and 27 received lymphadenectomy and completion thyroidectomy followed by radioactive iodine (LC&R group). The median follow-up time was 10.2 years. The overall survival, distant relapse-free survival, and lymph node relapse-free survival were not significantly different between the LC&R and L groups ($P = .89$, 0.58, and .22, respectively), whereas the LC&R group patients had significantly longer operation time, higher blood loss, and a higher rate of postoperative hypoparathyroidism compared with the L group ($P < .001$, respectively).

Conclusion: Compared with completion thyroidectomy and lymphadenectomy followed by radioactive iodine, lymphadenectomy alone was considered an acceptable therapeutic option which decreased the surgical disadvantages but did not decrease survival for at least 10 years after recurrence surgery for PTC patients with only lymph node recurrence.

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Introduction

Total thyroidectomy has been accepted worldwide as the primary initial surgical treatment for nearly all patients with papillary thyroid carcinoma (PTC),[1,2] and in Japan lobectomy is also considered an acceptable therapeutic option.[3,4] There is thus a large volume of data on PTC patients who underwent a lobectomy in Japan. Several studies, including analyses of the Surveillance, Epidemiology, and End Results database, have found no significant

differences between total thyroidectomy and lobectomy in terms of the overall survival (OS) or disease-specific survival in properly selected patients.[5,6]

In 2014, our group reported a 15-year cause-specific survival rate of 98.5% after a median follow-up of 17.6 years in PTC patients who had undergone a lobectomy.[4] Our report was cited in the British Thyroid Association guidelines (2014)[7] and the American Thyroid Association (ATA) guidelines (2015),[8] and lobectomy came to be considered a sufficient initial treatment, at least for low-risk PTC patients.

Considering the expected growth in the frequency of lobectomy as a treatment for PTC, the number of cases of postlobectomy recurrence may increase although the recurrence rate of PTC is very low. When PTC recurrence is identified at other organs (ie, distant

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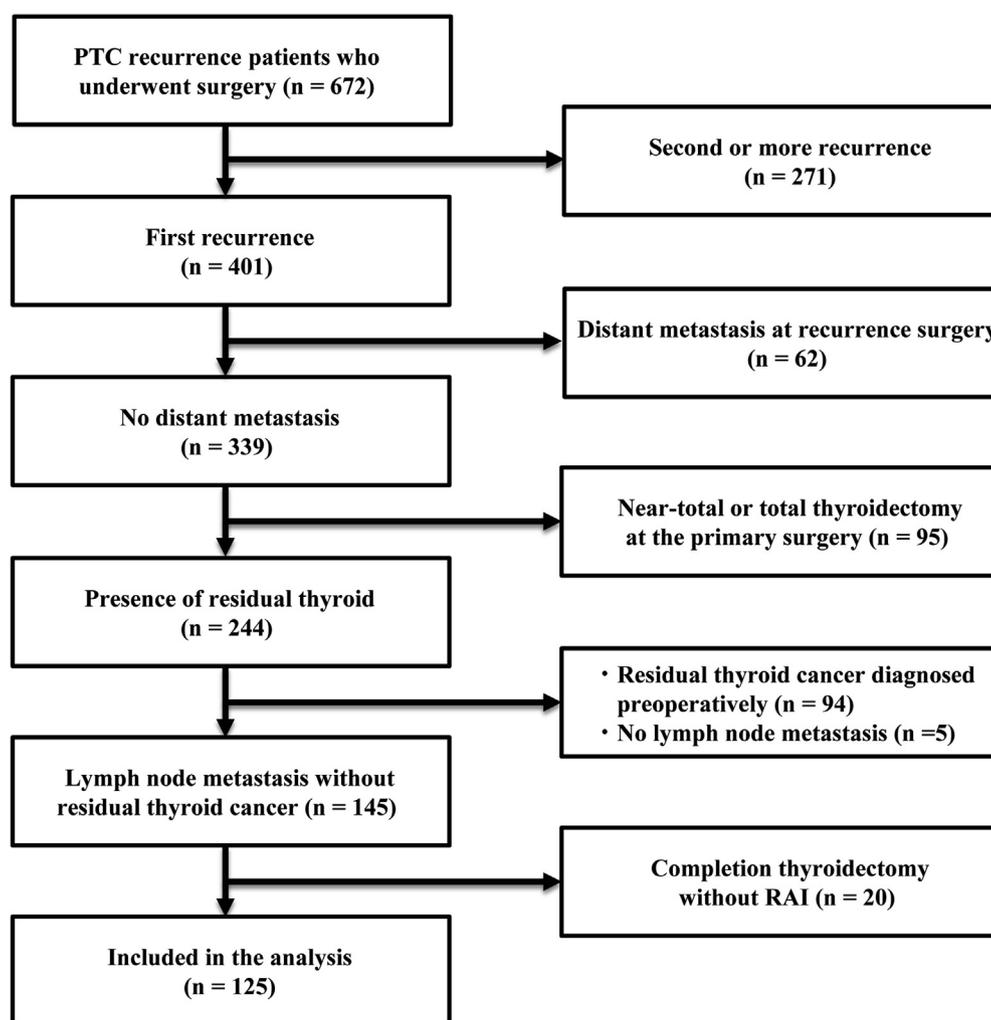E-mail address: k-matsuzu@ito-hospital.jp (K. Matsuzu).

Fig 1. Flow chart of the patient selection process.

metastasis), the standard treatment is radioactive iodine (RAI) ablation after a completion thyroidectomy. When PTC recurrence is detected at the residual thyroid, a completion thyroidectomy with or without RAI is usually performed. However, a standard treatment for postlobectomy lymph node recurrence has not been established, and it has not been determined which is the more appropriate treatment, lymphadenectomy alone or completion thyroidectomy and lymphadenectomy followed by RAI. We conducted the present study to address this question.

Methods

Patients

This was a retrospective study on PTC patients who underwent a lymphadenectomy for lymph node recurrence at Ito Hospital (Tokyo) during the 6-year period from January 2003 to December 2008. We reviewed the medical records of these patients after approval by the hospital's Ethics Committee (approval no. 169). In that period, 672 patients underwent surgery for PTC recurrence. The patient selection process is summarized in Figure 1. We excluded the patients whose recurrence surgery was for a second recurrence or more ($n = 271$). We also excluded patients with distant metastasis at the time of recurrence surgery, which included patients with distant metastasis diagnosed based on a

preoperative examination ($n = 62$) and those who underwent a total thyroidectomy at the primary surgery ($n = 95$). Patients were excluded if a malignancy in the residual thyroid was diagnosed preoperatively ($n = 94$), if they did not have lymph node metastasis at the time of recurrence surgery ($n = 5$), or if they did not undergo RAI ablation after a completion thyroidectomy for any reason, such as pregnancy or the refusal of RAI after surgery ($n = 20$).

The final study population consisted of 125 patients. These patients were informed of both treatment options (ie, lymphadenectomy only or completion thyroidectomy and lymphadenectomy followed by RAI) and the recommendation provided by their treating surgeon, and then were given their choice of treatment. For example, if they refused RAI for any reason (eg, because they wanted to bear children soon after surgery or were wary of the potential complications from completion thyroidectomy or the levothyroxine supplementation after surgery) they chose lymphadenectomy. If lymph node recurrence occurred in the lymph node dissection area of the initial surgery, swollen lymph nodes in this area were resected. And if lymph node recurrence occurred in the previously nondissected area, regional lymph node dissection was performed in the lymph node recurrence area. Patients who chose completion thyroidectomy underwent central neck dissection of the remnant lobe side along with completion thyroidectomy. When RAI remnant ablation was performed after completion thyroidectomy, patients received 30 mCi of I-131. Each patient was generally

Table I
Baseline characteristics of patients at the time of recurrence surgery

	Total n = 125	L group n = 98	LC&R group n = 27	P value
Age, y, median (IQR)	48 (33–65)	53 (35–66)	36 (30–52)	.004
Sex				.001
Male	24 (19)	13 (13)	11 (41)	
Female	101 (81)	85 (87)	16 (59)	
BMI (kg/m^2), median (IQR)	22.6 (20.7, 24.7)	22.6 (20.8, 24.7)	22.2 (19.7, 24.7)	.34
WHO performance status				.60
0 or 1	124 (99)	97 (99)	27 (100)	
2	1 (1)	1 (1)	0 (0)	
Time, y, from initial surgery to recurrence surgery, median (IQR)	4.5 (1.9–8.8)	4.7 (1.9–9.0)	4.5 (1.9–8.8)	.28
The largest diameter among metastatic LN				.59
<10 mm	18 (14)	14 (14)	4 (15)	
10–29 mm	102 (82)	81 (83)	21 (78)	
≥30 mm	5 (4)	3 (3)	2 (7)	
No. of preoperatively diagnosed metastatic LN, median (IQR)	2 (1, 3)	2 (1, 3)	2 (1, 3)	.35
Preoperatively diagnosed LN-recurrence sites				
In the LN dissection area of initial surgery	73 (58)	57 (58)	16 (59)	.92
On the contralateral side of primary tumor	39 (31)	28 (19)	11 (41)	.23
In the lateral neck	100 (80)	79 (81)	21 (78)	.74
Thyroglobulin levels, ng/mL	12.0 (4.7–40.4)	11.5 (4.8–32.0)	28 (3.5–52.4)	.17
RLNP before recurrence surgery (the side of initial surgery)	22 (18)	18 (18)	4 (15)	.67
Diagnoses				
Hypertension	27 (22)	21 (22)	6 (22)	.93
Cardiovascular disease	9 (7)	7 (7)	2 (7)	.96
Diabetes	4 (3)	4 (4)	0 (0)	.29
Depression	2 (2)	1 (1)	1 (4)	.33

Data are presented as a number (%) or median (IQR). L group: patients who underwent lymphadenectomy without completion thyroidectomy. LC&R group: patients with lymphadenectomy and completion thyroidectomy followed by RAI ablation.
BMI, body mass index; *LN*, lymph node; *WHO*, World Health Organization.

surveyed by the following strategy. Patient visits were performed every 6 months. A neck ultrasound and blood tests were performed at each visit. Chest x-ray was performed at a periodic health check-up every year. Computed tomography examination of the chest was performed before recurrence surgery and every 5 years post-operatively. Additional computed tomography examination was performed for the patients diagnosed with lymph node recurrence by ultrasound or suspected of recurrence based on changes in their serum thyroglobulin (Tg) levels.[4]

Assessment parameters and statistical analyses

To evaluate the impact of RAI ablation after completion thyroidectomy on patients with lymph node recurrence of PTC, we classified the patients into 2 groups: an L group of patients who had undergone only a lymphadenectomy (without completion thyroidectomy; n = 98), and an LC&R group of patients who had undergone lymphadenectomy and completion thyroidectomy followed by RAI ablation (n = 27). The outcome data included surgical outcomes, distant relapse-free survival, lymph node relapse-free survival, and the details of OS. Permanent hypoparathyroidism was defined as the need to continue any calcium or vitamin D supplementation 12 months after recurrence surgery. The overall cost of each treatment was defined as the total treatment cost for 1 year after recurrence surgery, including surgery, RAI, and medication cost. Extra costs for an amenity bed and the cost of meals during hospitalization were excluded from the overall cost. The cost in US dollars was calculated at a yen-dollar conversion rate of 110 yen to 1 US dollar.

Statistical analyses were conducted using STATA software version 13.0 (Stata Corporation, College Station, TX). Pearson's χ^2 test was used for the comparison of categorical variables. Student *t* test and the Mann-Whitney *U*-test were used to compare continuous variables. The OS rates were estimated using the Kaplan-Meier method and compared using stratified log-rank tests.

Results

Patient characteristics

The median follow-up time was 10.2 years (10.0 years in the L group and 9.8 years in the LC&R group). As shown in Table I, most of the baseline characteristics of the L and LC&R patients were similar at the time of recurrence surgery, aside from age and sex. The L group patients were 13 men and 85 women, with a median age of 53 years. The LC&R group patients were 11 men and 16 women, with a median age of 36 years. There were no significant differences between the 2 groups in body mass index, the median time from initial surgery to recurrence surgery, the largest diameter among the metastatic lymph nodes, the number of preoperatively diagnosed metastatic lymph nodes, lymph node recurrence sites (recurrence in the lymph node dissection area of the initial surgery, on the contralateral side of primary tumor, or in the lateral neck), Tg level, the recurrent laryngeal nerve paralysis (RLNP) of the side of the initial surgery before recurrence surgery, or comorbidities (ie, hypertension, cardiovascular disease, diabetes, and depression, which RAI can affect).

Table II summarizes the characteristics of the patients at initial surgery. There were no significant differences between the L and LC&R groups in terms of the percentage of patients ≥55 years of age at the initial surgery, the presence of gross extrathyroidal extension with the exception of only strap muscles, multifocal PTC, the number of positive lymph nodes, or stage according to the American Joint Committee on Cancer eighth edition.[9] Although thyroid-stimulating hormone (TSH) is strongly recommended for high-risk thyroid cancer patients, a prospective study showed that disease-free survival for low-risk patients without TSH suppression was not inferior to that of patients with TSH suppression.[8,10] The rates of complete TSH suppression (<0.10 mIU/L) after initial surgery were not significantly different (21% and 15% for the L and LC&R group; P = .45).

Table II
Characteristics of the patients at their initial surgery

	Total n = 125	L group n = 98	LC&R group n = 27	P value
Age, y				
<55	91 (73)	68 (69)	23 (85)	.10
≥55	34 (27)	30 (31)	4 (15)	
Gross ETE (exception: strap muscles)	14 (11)	10 (10)	4 (15)	.50
Multifocal PTC	50 (40)	40 (41)	10 (37)	.72
No. of metastatic LN, median (IQR)	5 (1, 13)	5 (1, 11)	5 (0, 18)	.95
Stage (AJCC 8th)				.76
Stage I or II	119 (95)	93 (95)	26 (96)	
Stage III	6 (5)	5 (5)	1 (4)	
Lymph node dissection	121 (97)	96 (98)	25 (93)	.16
PTC subtype				
Papillary carcinoma	99 (79)	81 (83)	18 (67)	
Papillary microcarcinoma	15 (12)	10 (10)	5 (19)	
Follicular variant of PTC	6 (5)	4 (4)	2 (7)	
Diffuse sclerosing variant of PTC	3 (2)	1 (1)	2 (7)	
Clear cell variant of PTC	1 (1)	1 (1)	0 (0)	
Encapsulated variant of PTC	1 (1)	1 (1)	0 (0)	

Data are presented as a number (%).
AJCC, American Joint Committee on Cancer; *ETE*, extrathyroidal extension; *LN*, lymph node.

Table III
Comparison of surgical outcomes between the L and LC&R groups

	Total n = 125	L group n = 98	LC&R group n = 27	p
Operation time, min, median (IQR)	48 (28–75)	39 (24–58)	83 (63–100)	<.001*
Operative blood loss, ml, median (IQR)	35 (12–89)	27 (9–57)	102 (55–173)	<.001*
No. of total harvested LN, median (IQR)	7 (2–21)	5 (2–18)	18 (6–24)	.003
Ratio of metastatic LN to total harvested LN (%), median (IQR)	40 (17–100)	40 (17–100)	39 (19–67)	.44
Postoperative complications:				
Hypoparathyroidism	15 (12)	2 (2)	13 (48)	<.001*
Permanent hypoparathyroidism	11 (9)	1 (1)	10 (37)	<.001*
RLNP occurring after recurrence surgery	2 (2)	1 (1)	1 (4)	.33
Overall treatment cost for 1 y after recurrence surgery, US $, mean ± SD	4317 ± 2248	3519 ± 1726	7215 ± 1366	<.001*

Data are presented as a number (%), mean ± SD, or median (IQR).
Permanent hypoparathyroidism was defined as the need to continue any calcium or vitamin D supplementation 12 months after recurrence surgery. The cost in US dollars was calculated at a yen-dollar conversion rate of 110 yen to 1 US dollar.
LN, lymph node; *SD*, standard deviation.
* $P < .001$.

Surgical outcomes of recurrence surgery

The results of our comparison of surgical outcomes in the 2 groups are provided in Table III. The operation time was significantly longer in the LC&R group compared with the L group (median 83 for interquartile range [IQR] 63–100 min vs median 39 for IQR 24–58 min; $P < .001$). Blood loss was also significantly higher in the LC&R group (median 102 for IQR 55–182 mL vs median 27 for IQR 9–57 mL; $P < .001$). Although there was no significant difference between the L and LC&R groups in terms of the ratio of the number of metastatic lymph nodes to the total number of harvested lymph nodes, the total number of harvested lymph nodes was significantly higher in the LC&R group compared with the L group (median 18 for IQR 6–24 vs median 5 for IQR 12–18 min; $P = .003$). The rate of postoperative permanent hypoparathyroidism was significantly higher in the LC&R group (37% vs 1%; $P < .001$). Because RLNP occurred after recurrence surgery in only a few patients, there was no significant difference between the groups in this parameter. The overall treatment cost was significantly higher in the LC&R group compared with the L group ($7,215 ± $1,366 vs $3,519 ± $1,726; $P < .001$), although the treatment costs varied between countries and the cost data were limited in Japan.

Survival and relapse outcomes after recurrence surgery

Figure 2, *A* shows the Kaplan-Meier survival curves for the L and LC&R groups after recurrence surgery. The patients with recurrence surgery in this series had good prognoses, and the 10-year overall survival rates were 95.5% ± 4.4% and 97.8% ± 1.6% in the LC&R and L groups, respectively. The survival rate was not significantly different between the 2 groups ($P = .89$; log-rank test).

Figure 2 also provides the Kaplan-Meier survival curves of the patients who remained free of distant relapse (Fig 2, *B*) and lymph node relapse after recurrence surgery (Fig 2, *C*). Distant metastases were rare in both groups, and the 10-year distant relapse-free survival rates were 91.7% ± 5.7% and 91.0% ± 3.0% in the LC&R and L groups, respectively. On the other hand, second lymph node recurrence occurred more frequently after recurrence surgery, and the 10-year lymph node relapse-free survival rates of the LC&R and L groups were 66.8% ± 10.1% and 76.5% ± 4.5%, respectively. Among patients with second lymph node recurrence, 22.2% and 19.0% in the LC&R and L groups did not undergo an operation, respectively. The distant relapse-free survival rate and the lymph node relapse-free survival rate did not differ significantly between the 2 groups ($P = .58$ and 0.22, respectively; log-rank test).
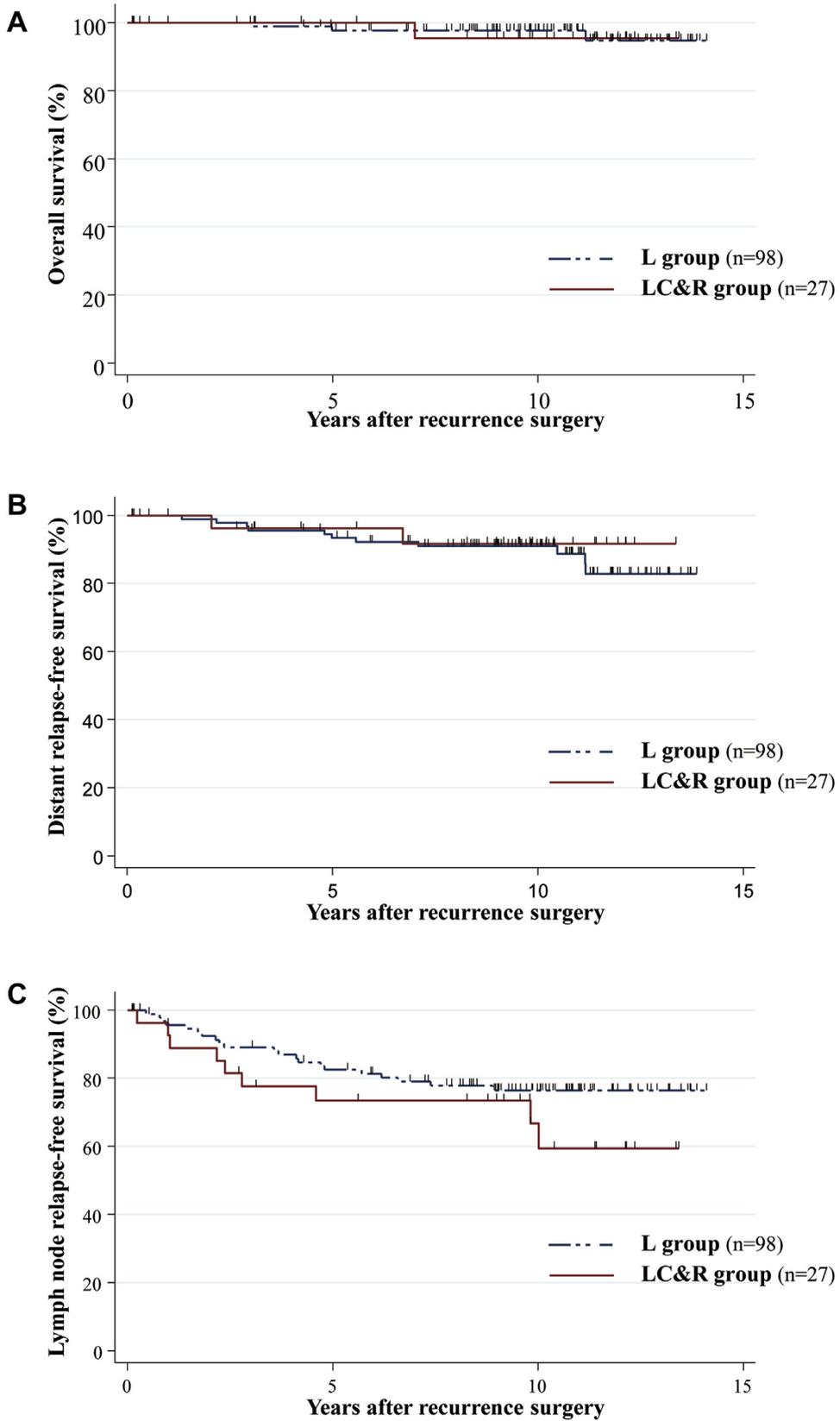
Fig 2. Overall survival (*A*), distant relapse-free survival (*B*), and lymph node relapse-free survival (*C*) curves for the L group and the LC&R group after recurrence surgery.

Discussion

For the past several decades, total thyroidectomy has been standard initial surgical treatment for primary PTC,[1,2] while

recently the application range of lobectomy for PTC was broadened in ATA, British Thyroid Association, and the Japanese Society of Thyroid Surgeons/Japanese Association of Endocrine Surgeons guidelines.[3,7,8] In Japan, lobectomy for PTC has been performed for

years, but this approach is still relatively new in North America and Europe. Therefore, in the near future, opportunities to treat recurrence after lobectomy will be increased in North America and Europe. In this study, we explored the clinical status of patients with lymph node recurrence after lobectomy who underwent lymphadenectomy alone or a combination therapy of completion thyroidectomy and lymphadenectomy followed by RAI. PTC is a slow-growing tumor with 10-year relative survival rates >93%.[11-13] The 10-year recurrence rate of PTC after surgery is also low at 9.4%.[14] Our present analyses revealed that patients who underwent surgery for lymph node recurrence had good prognoses, and the OS and distant relapse-free survival rates were similar for lymphadenectomy alone and completion thyroidectomy and lymphadenectomy followed by RAI.

The lymph node recurrence rate after primary surgery for PTC has been reported to be between 5% and 20%.[13] In our series, the lymph node re-recurrence rate was high, suggesting that cases of lymph node recurrence need careful follow-up with lymph node re-recurrence surveillance. Because it is difficult to control lymph node metastasis with RAI, surgery with curative intent is the recommended treatment for lymph node recurrence.[7,13] There are few reports about RAI after surgery for lymph node recurrence, but Yim et al reported that adjuvant RAI therapy after reoperation for localized neck recurrence in patients who had already undergone an initial total thyroidectomy demonstrated no benefit.[8,15] Piccardo et al reported that adjuvant RAI therapy after reoperation for localized neck recurrence in patients who had undergone an initial total thyroidectomy was associated with better progression-free survival only in patients with Tg levels ≥1 ng/mL under TSH suppression in a series of 52 patients with Tg levels ≥1 ng/mL and 61 patients with Tg levels <1 ng/mL.[16] In the present study, the frequency of lymph node re-recurrence was high in both the L and LC&R groups with no significant difference, suggesting that adjuvant RAI therapy after recurrence surgery does not diminish the incidence of lymph node re-recurrence.

As expected, our study showed the disadvantages of completion thyroidectomy for adjuvant RAI therapy: prolonged operation times, increased blood loss, and a high rate of postoperative hypoparathyroidism. These results are reasonable in light of the fact that the patients in the LC&R group underwent a completion thyroidectomy in addition to lymphadenectomy, whereas the patients in the L group underwent only a lymphadenectomy. This fact may also explain why the total number of harvested lymph nodes was high in the LC&R group. For patients with RLNP on the side of the initial surgery before recurrence surgery, treatment with lymphadenectomy alone may be more likely to prevent the need for a tracheotomy after bilateral RLNP compared with completion thyroidectomy, although the rates of postoperative RLNP were not significantly different between our present L and LC&R groups.

Our study also showed another important disadvantage of RAI therapy: the operative and other costs. In general, the costs and benefits of therapeutic options should be considered. For example, in Japan, a lymphadenectomy with completion thyroidectomy costs approximately 8 to 20 times more than lymphadenectomy alone: $2,198 US dollars (¥241,800) for lymphadenectomy with completion thyroidectomy versus $109 to $262 US dollars (¥12,000–28,800) for a lymphadenectomy only. The cost of adjuvant RAI therapy includes $412 US dollars (¥45,360) for the iodine radioisotope I-131, $1,923 US dollars (¥211,576) for recombinant human TSH, and other costs (such as the cost of scintigraphies and the RAI management fee). In Japan, all patients are eligible for treatment through the national health-insurance system, and each cost of the medical treatment is fixed at a relatively reasonable value by the system. However, the fact that each treatment cost in Japan was different from its counterpart in other countries limited the cost comparison in the present study. The contraception period after RAI is also an important factor in the selection of patients with lymph node recurrence. In fact, several patients who were excluded from the present series were pregnant and thus did not undergo RAI ablation after completion thyroidectomy.

Major potential advantages of completion thyroidectomy and lymphadenectomy followed by RAI are the diagnostic scanning for metastases that are not identified by preoperative imaging tests and the utility of serum Tg measurement.[7,8] A remnant lobe limits the ability to follow serum Tg after surgery, although serum Tg measurement has been reported to be of value in detecting recurrence after lobectomy.[17] In our study, although we could not rule out the possibility that a few patients in the L group had micro distant metastasis that could be identified by RAI but not by CT scan, there were no clinical problems in this series related to any such failure of identification. In fact, no patient in the LC&R group was found to have distant metastasis by RAI ablation after completion thyroidectomy, and both groups showed good prognosis.

Despite our encouraging results, some study limitations should be noted. (1) This retrospective study may have had confounding or selection biases because the treatments were not randomly assigned in this patient population; (2) type 2 error could not be avoided owing to the small size of the study population; and (3) the effect of the treatments selected for the re-recurrence cases was not considered. The patients were not randomly assigned to the groups and the significant difference in age between the 2 groups (Table I) could have been a relevant bias. We are not sure why this difference occurred because it is our institutional policy not to select treatment options (ie, lymphadenectomy only or completion thyroidectomy and lymphadenectomy followed by RAI) by age or sex. One possibility is that the treating surgeon might not have strongly recommended RAI to elderly patients because advancing age reduces RAI sensitivity.[18] Age at local recurrence is considered to have an impact on survival. Several studies have reported that patients less than 45 years of age had better prognosis.[19–21] In this study, the LC&R group was significantly younger than the L group, and therefore, the LC&R group might have had the potential for better prognosis, assuming that there is no difference in outcome between therapy with lymphadenectomy alone and treatment with completion thyroidectomy and lymphadenectomy followed by RAI. However, the survival rate was not significantly different between the 2 groups. This fact suggests that therapy with lymphadenectomy alone is not inferior to treatment with completion thyroidectomy and lymphadenectomy followed by RAI in terms of survival.

The >90% rate of lymph node dissection at the time of the initial operation does not match the current ATA recommendations. The 2015 ATA guidelines recommended thyroidectomy without prophylactic central neck dissection for T1/T2, noninvasive, clinically node-negative (cN0) PTC.[8] However, the 2006 ATA guidelines recommended routine central-compartment neck dissection for all PTC.[22] The patients in our study series underwent recurrent surgery from 2003 to 2008 and initial surgery before then. This is one reason why the rate of lymph node dissection at the time of the initial operation was high. Although the value of routine prophylactic central neck dissection for cN0 disease remains unclear, prophylactic central neck dissection may have little effect on the prognosis for T1/T2, noninvasive, cN0 PTC. Therefore, it is thought that prophylactic central neck dissection for T1/T2, noninvasive, cN0 PTC in our series did not affect outcome.

Although the number of preoperatively diagnosed metastatic lymph nodes did not differ between our 2 patient groups, the total number of harvested lymph nodes was higher in the LC&R group than the L group. These results are reasonable in light of the fact

that the total number of harvested lymph nodes from patients of the LC&R group included the lymph nodes from central neck dissection of the remnant lobe side along with completion thyroidectomy, in addition to those from lymphadenectomy of preoperatively diagnosed metastatic lymph nodes. As in the case of prophylactic central neck dissection at the initial surgery, this fact may explain why the number of harvested metastatic lymph nodes in the LC&R group was high and might indicate that prophylactic central neck dissection of the remnant lobe side does not affect outcome.

The optimum follow-up period for PTC is less certain because PTC is a slow-growing tumor. The median period between the initial surgery and the recurrence surgery in this patient series was ≈5 years, and the median follow-up time was ≈10 years: that is, the total follow-up period after the initial surgery was ≈15 years. This is a realistic follow-up period that a single hospital may achieve for PTC patients, and thus our 15 years of follow-up data was suggested to be adequate for the selection of treatments. Although it has been reported that PTC has little potential for recurrence even 20 years after initial surgery,[4] our findings should be verified by future trials with greater long-term follow-up in order to validate the benefits of each therapy at 20, 30, and more years after recurrent surgery.

It is natural for some physicians to favor aggressive treatments, such as completion thyroidectomy followed by RAI, for their patients with PTC recurrence. In these updated analyses, however, we found that in PTC patients who had lymph node recurrence with a normal remnant lobe, there were no significant differences in overall survival, distant relapse-free survival, or lymph node relapse-free survival between a combination approach using completion thyroidectomy and lymphadenectomy followed by RAI and an approach using lymphadenectomy alone (median follow-up >10 years). Moreover, completion thyroidectomy and lymphadenectomy followed by RAI resulted in a significant increase in the rate of surgical complications such as postoperative hypoparathyroidism. For these reasons, lymphadenectomy alone can be considered an acceptable treatment option for PTC patients with only lymph node recurrence for at least the first 10 years after recurrence surgery.

Conflict of interest

The authors report no conflicts of interest in this work.

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