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ORIGINAL SCIENTIFIC REPORT

Long-Term Outcomes After Lobectomy for Patients with High-Risk Papillary Thyroid Carcinoma

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Abstract

Background Guidelines universally recommend total thyroidectomy for high-risk papillary thyroid carcinoma (PTC). However, in Japan, thyroid-conserving surgery had been widely applied for such patients until recently. We investigated long-term outcomes for this strategy.

Methods A prospectively recorded database was retrospectively analyzed for 368 patients who had undergone curative surgery for high-risk PTC without distant metastasis between 1993 and 2013. High-risk PTC was defined for tumors showing tumor size > 4 cm, extrathyroidal extension, or large nodal metastasis ≥ 3 cm.

Results Median age was 59 years and 243 patients were female. Mean duration of follow-up was 12.7 years. Lobectomy was conducted for 207 patients (LT group) and total or near-total thyroidectomy for 161 patients (TT group). The frequency of massive extrathyroidal invasion and large nodal metastasis was lower in the LT group than in the TT group. After propensity score matching, no significant differences were seen between groups for overall survival, cause-specific survival or distant recurrence-free survival. In the overall cohort, multivariate analysis identified age ≥ 55 years, large nodal metastasis, tumor size > 4 cm and massive extrathyroidal invasion as significantly associated with cause-specific survival, whereas extent of thyroidectomy was not.

Conclusions For patients with high-risk PTC without distant metastasis, curative surgery with lobectomy showed almost identical oncological outcomes compared to total thyroidectomy. The benefits of total thyroidectomy for high-risk PTC should be reevaluated in the future prospective studies.

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Abbreviations

PTC	Papillary thyroid carcinoma
RAI	Radioactive iodine
TSH	Thyroid-stimulating hormone
JAES	Japan association of endocrine surgery
CIH	Cancer institute hospital
LT group	Lobectomy group
TT group	Total or near-total thyroidectomy group
CT	Computed tomography
OS	Overall survival
CSS	Cause-specific survival
MRFS	Distant recurrence-free survival
QOL	Quality of life
DTC	Differentiated thyroid carcinoma

Introduction

Patients with papillary thyroid carcinoma (PTC) generally experience a favorable prognosis, but some exhibit local invasion or extensive metastasis and die of the disease. Total thyroidectomy followed by radioactive iodine (RAI) therapy and thyroid-stimulating hormone (TSH) suppression therapy used be the mainstay of treatment for PTC in Western countries. In contrast, the majority of patients with PTC in Japan had been treated by thyroid-conserving surgery (lobectomy or subtotal thyroidectomy) [1]. Several studies proposing risk-group classification systems predicting cancer recurrence or mortality [2–4] have shown excellent treatment outcomes for low-risk PTC regardless of the therapeutic strategy [5–8]. Recently, the concept of risk-adapted management has become highly valued and less-aggressive approaches using thyroid lobectomy without adjuvant therapies have been approved for low- or intermediate-risk PTC. On the other hand, guidelines universally recommend total thyroidectomy for patients with high-risk PTC [3, 9–11]. This policy may be associated with a higher rate of surgical complications, but has advantages in the management of high-risk PTC. That is, patients can be directly treated using RAI, and recurrences are easily evaluated by thyroglobulin follow-up. However, few reports have shown definite superiority of total thyroidectomy over lobectomy in terms of the survival of high-risk PTC patients [12, 13].The aim of the study was to clarify the long-term treatment outcomes of curative surgery with lobectomy compared with total or near-total thyroidectomy for patients with high-risk PTC without distant metastasis at a Japanese tertiary oncology referral center.

Materials and methods

Patients

We retrospectively reviewed the prospectively accumulated database of consecutive 1,467 patients who underwent primary thyroid surgery for PTC > 1 cm in diameter at Cancer Institute Hospital (CIH) between 1993 and 2013. Guidelines from the Japan Association of Endocrine Surgery (JAES) [10] define high-risk PTC as a tumor displaying at least one of the following clinical features: (1) tumor size > 4 cm; (2) extrathyroidal extension or extranodal extension to adjacent structures other than the sternothyroid muscle; (3) clinical lymph node metastasis > 3 cm; or (4) distant metastasis detected on imaging studies. The definition is very similar to the 2015 American Thyroid Association guidelines [3] where high-risk PTC was defined as (1) macroscopic invasion of tumor into the perithyroidal soft tissues; (2) incomplete tumor resection; (3) distant metastasis; (4) postoperative serum thyroglobulin suggestive of distant metastasis; or (5) nodal metastasis with ≥ 3 cm in largest diameter. In this study, 509 patients were classified to the high-risk group according to the JAES definition. After exclusion of patients who showed initial distant metastasis, underwent non-curative surgery and had subtotal thyroidectomy or isthmusectomy, a total of 368 patients were finally included in the study cohort (Fig. 1). Median age at initial surgery was 59 years, and 243 patients were female. Among these, lobectomy was conducted for 207 patients (56.2%; LT group) and total or near-total thyroidectomy for 161 patients (43.8%; TT group). Seventeen patients (8.2%) in LT group subsequently underwent completion thyroidectomy.

We investigated genetic molecular profiles including *BRAF V600E* mutation and *TERT* promoter mutations (C228T and C250T) for 158 patients in the overall cohort. The procedure for these analyses has been described previously [14].

Treatment methods

Until 2004, we performed total thyroidectomy only for patients with bilateral disease or distant metastasis. During the period, we tried to perform curative surgery with lobectomy (or subtotal thyroidectomy) even for high-risk cases in an attempt to preserve thyroid function, when a tumor was confined to one lobe and no distant metastasis was present. RAI therapy was conducted for patients who developed distant recurrence followed by completion thyroidectomy if needed.

In 2004, we developed our original risk-group classification system (CIH classification) for predicting cause-

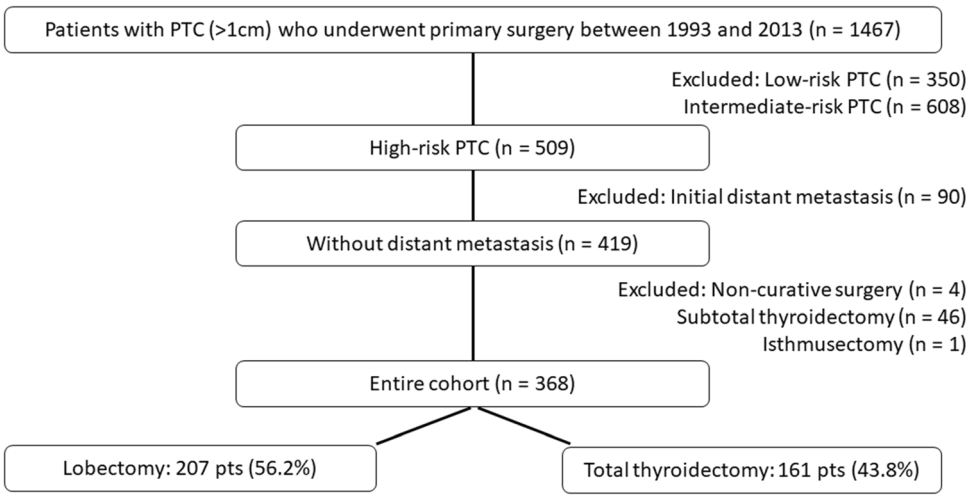

Fig. 1 Study cohort Risk-group stratification was conducted according to the Japan Association of Endocrine Surgery guidelines in 2018.Among the lobectomy group, 17 patients (8.2%) underwent completion total thyroidectomy afterward. Of the total thyroidectomy group, 27 patients had near-total thyroidectomy. PTC, papillary thyroid carcinoma

specific mortality from PTC [4]. Patients with distant metastasis and older patients (≥ 50 years) with massive extrathyroidal invasion or large nodal metastasis (≥ 3 cm) were defined as high-risk, while all other patients were as low-risk. Here, we defined only patients who had preoperative recurrent laryngeal nerve palsy or transluminal invasion of the trachea and/or esophagus as showing massive extrathyroidal invasion [15]. From 2005 onward, we have recommended total thyroidectomy and RAI therapy for patients who come under the high-risk category according to the CIH classification. Meanwhile, the extent of thyroidectomy has been determined based on the choices of the individual patient when unilateral low-risk PTC is diagnosed by the system [5]. The CIH classification adopted a narrower criterion for high-risk PTC compared to the JAES definition. Thus, some JAES high-risk patients were CIH low-risk PTC, and treated by lobectomy even in this period.

We conducted lymph node dissection based on the following policy: (1) dissection of the central compartment alone for patients with lymph node metastasis only in the central zone or with no lymph node metastasis; and (2) lateral neck dissection if the patient was diagnosed with lateral neck lymph node metastasis [16]. When adjacent structures were invaded by cancer, the intent was curative surgery with radical resection of the invaded organs and reconstruction if needed.

Most ^{131}I treatments were initially conducted with 30–100 mCi and repeated doses of 100–120 mCi to a cumulative dose of 600 mCi, as appropriate. However, some patients were judged as RAI-refractory after whole-body scanning with only 5 mCi. Treatment with multikinase inhibitors, namely, sorafenib or lenvatinib, has been provided since 2012 for patients with unresectable, RAI-refractory progressive disease.

Follow-up and evaluation

Physical examination, chest X-ray or lung computed tomography (CT), in addition to neck ultrasonography, were performed every 6 months in the first 3 years and annually thereafter. Recurrence was defined as structural disease confirmed by either cytological or pathological examination for cervical disease. Hematogenous metastasis was diagnosed from imaging studies (CT, ^{131}I scintigraphy, etc.). Thyroglobulin and anti- thyroglobulin antibodies were measured periodically, but biochemical abnormalities alone were not regarded as recurrence. For all deceased patients, cause of death was confirmed by death certificates obtained from municipal records. Mean duration of follow-up was 12.7 ± 5.7 years.

Statistical analysis

Comparisons between groups were performed using Fisher's exact test for categorical variables and the Mann–Whitney U test for continuous variables. Survival curves were determined using Kaplan–Meier methods and compared by log-rank testing. Multivariate analysis was carried out by Cox proportional hazard modeling incorporating factors that had been validated as important prognostic factors for PTC and extent of thyroidectomy. For propensity score matching, patients in the LT and TT groups were matched by age, sex, tumor size, presence of massive extrathyroidal invasion, and large nodal metastasis in a 1:1 ratio. The caliper width was set as 0.05. All analyses were performed using EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan) [17]. Values of $p < 0.05$ were considered statistically significant.

Results

Clinical and molecular characteristics for the entire cohort are shown in Table 1, comparing LT and TT groups. Age, sex, tumor size and frequencies of *BRAF V600E* and *TERT* promoter mutations were identical between groups. Rates of massive extrathyroidal invasion, multiple lesions of PTC and large nodal metastasis were significantly lower in the LT group than in the TT group. Wider extent of lymph node dissection and resection of invaded adjacent organs were more frequent in the TT group. RAI treatment was carried out for 81 patients (50.3%) of the TT group. Three of them were treated after development of recurrence. On the other hand, 14 patients (6.8%) in the LT group had the therapy following completion total thyroidectomy afterward.

Treatment outcomes for the entire cohort are summarized in Table 2. 10-year overall survival (OS) and cause-specific survival (CSS) rates were 79.2% and 89.5%, respectively. Recurrence developed in 136 patients. In the LT group, only 2 patients (1.0%) showed recurrence at the remnant thyroid. Kaplan–Meier curves for OS, CSS and distant recurrence-free survival (MRFS) comparing the LT and TT groups are shown in Fig. 2. OS rates did not differ between groups, but CSS and MRFS rates were significantly better in the LT group than in the TT group.

Propensity score matching for the overall cohort yielded a total of 104 matched pairs. This cohort showed no significant differences in any clinical or molecular factors between groups, aside from multiplicity (Table 3). After matching, no significant differences in OS (10-year OS, 76.5% vs. 82.5%, $p = 0.36$), CSS (10-year CSS, 89.7% vs. 88.8%, $p = 0.76$) or MRFS (10-year MRFS, 78.7% vs. 752%, $p = 0.72$) were evident between the LT group and the TT group (Fig. 3).

In the overall cohort, prognostic factors for CSS and MRFS other than extent of thyroidectomy were evaluated by univariate analysis (Table 4). Patients with age ≥ 55 years, massive extrathyroidal invasion, large nodal metastasis and *TERT* promoter mutation experienced significantly worse CSS than their counterparts. Moreover, Cox proportional hazards modeling identified older age, large tumor, massive extrathyroidal invasion and large nodal metastasis as independent risk factors for worse CSS, and older age, massive extrathyroidal invasion and large nodal metastasis as independent risk factors for worse MRFS.

Table 1 Characteristics of patients with high-risk papillary thyroid carcinoma without initial distant metastasis; entire cohort

	Total (n = 368)	Lobectomy (n = 207)	Total thyroidectomy (n = 161)	P value[f]
Patient and tumor characteristics				
Median age at initial surgery (years)	59 (range, 15–89)	58 (range, 15–89)	59 (range, 16–81)	0.53
Age ≥ 55 years	216 (58.7%)	114 (55.1%)	102 (63.4%)	0.14
Female sex	243 (66.0%)	133 (64.3%)	110 (68.3%)	0.44
Median tumor size (mm)	35 (range, 11–115)	35 (range, 11–115)	35 (range, 11–120)	0.69
Tumor size > 4 cm	137 (37.2%)	80 (38.6%)	57 (35.4%)	0.59
Extrathyroidal extension[a]	249 (67.7%)	133 (64.3%)	116 (72.0%)	0.12
Massive extrathyroidal invasion[b]	100 (27.2%)	35 (16.9%)	65 (40.4%)	< 0.0001
Multiplicity	175 (47.6%)	75 (36.2%)	100 (62.1%)	< 0.0001
Large nodal metastasis ≥ 3 cm	128 (34.8%)	53 (25.6%)	75 (46.6%)	< 0.0001
BRAF V600E mutation[c]	131 (82.9%)	61 (81.3%)	70 (84.3%)	0.68
TERT promoter mutation[c]	62 (39.2%)	32 (42.7%)	30 (36.1%)	0.42
Treatment methods				
Central compartment dissection[d]	131 (35.6%)	96 (46.3%)	35 (21.7%)	< 0.0001
Lateral compartment dissection	231 (62.8%)	105 (50.7%)	126 (78.3%)	
Resection of the adjacent organ (s)	263 (71.5%)	137 (66.2%)	126 (78.3%)	0.014
Radioactive iodine therapy[e]	95 (25.8%)	14 (6.8%)	81 (50.3%)	< 0.0001
Multikinase inhibitor therapy	10 (2.7%)	3 (1.4%)	7 (4.3%)	0.11

[a]T4a or T4b tumor according to the AJCC/UICC TNM classification, 8th edition

[b]Patients who had preoperative recurrent laryngeal nerve palsy or transluminal invasion of the trachea and/or esophagus

[c]Among 368 patients, 158 were examined

[d]Six patients in the lobectomy group did not undergo any lymph node dissection

[e]Patients in lobectomy group received radioactive iodine therapy following completion total thyroidectomy afterward

[f]p-values were calculated using Mann–Whitney's U test or Fisher's exact test, as appropriate

Table 2 Treatment outcomes of patients with high-risk papillary thyroid carcinoma without initial distant metastasis; entire cohort

	Total (n = 368)	Lobectomy (n = 207)	Total thyroidectomy (n = 161)	p value[a]
All-cause death	109 (29.6%)	60 (29.0%)	49 (30.4%)	
10-year overall survival rate	79.2%	80.7%	77.4%	0.37
Cause-specific death	51 (13.9%)	23 (11.1%)	28 (17.4%)	
10-year cause-specific survival rate	89.5%	93.2%	84.7%	0.049
Recurrence	136 (37.0%)	71 (34.3%)	65 (40.4%)	
Lymph node (s)	104 (28.3%)	55 (26.6%)	49 (31.0%)	
Remnant thyroid	2 (0.5%)	2 (1.0%)	0 (0%)	
Other neck region	25 (6.8%)	10 (4.8%)	15 (10.6%)	
Distant site	84 (22.8%)	38 (18.4%)	46 (28.6%)	
10-year distant recurrence-free survival	75.1%	80.1%	68.7%	**0.026**

[a]p-values were calculated using the log-rank test

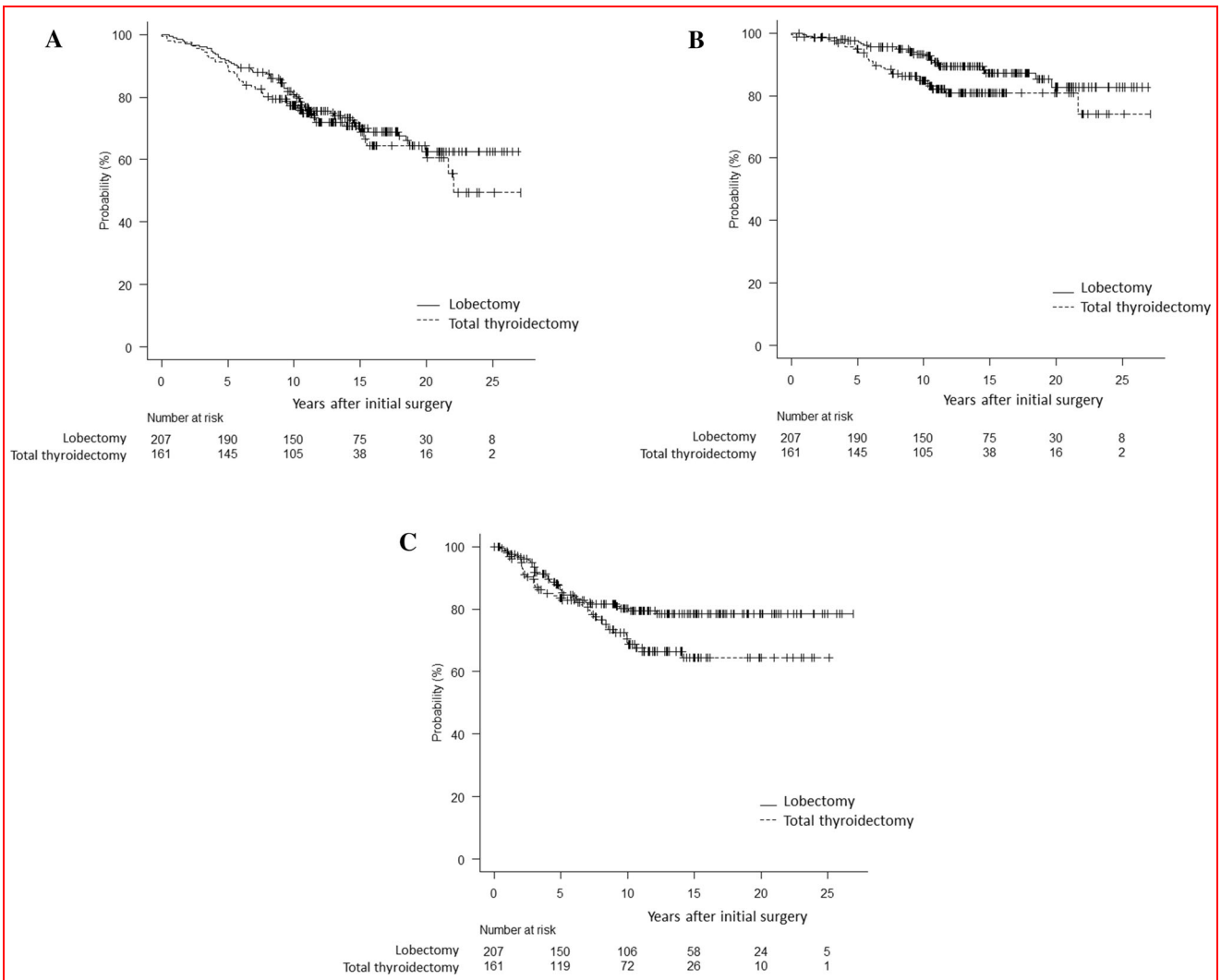

Fig. 2 Extent of thyroidectomy and treatment outcomes for high-risk PTC without initial distant metastasis, the entire cohort **a** Overall survival **b** Cause-specific survival **c** Distant recurrence-free survival PTC, papillary thyroid carcinoma

Table 3 Characteristics of patients with high-risk papillary thyroid carcinoma without initial distant metastasis after matching

	Lobectomy (n = 104)	Total thyroidectomy (n = 104)	p value[c]
Patient and tumor characteristics			
Median age at initial surgery (years)[a]	58.5 (range, 20–84)	57 (range, 16–81)	0.69
Female sex[a]	74 (71.2%)	67 (64.4%)	0.37
Median tumor size (mm)[a]	28 (range, 11–92)	32 (range, 11–90)	0.29
Extrathyroidal extension	71 (68.3%)	69 (66.3%)	0.88
Massive extrathyroidal invasion[a]	27 (26.0%)	27 (26.0%)	1.00
Multiplicity	44 (42.3%)	69 (66.3%)	0.00079
Large nodal metastasis $\geq$ 3 cm [a]	43 (41.3%)	43 (41.3%)	1.00
BRAF V600E mutation[b]	26 (83.9%)	44 (81.5%)	1.00
TERT promoter mutation[b]	16 (51.6%)	20 (37.0%)	0.26

[a]Factors selected for matching

[b]Among 208 patients, 85 were examined

[c]p-values were calculated using Mann–Whitney's U test, or Fisher's exact test, as appropriate

However, extent of thyroidectomy showed no significant correlations with CSS or MRFS (Table 5).

Discussion

Recent publications and guidelines have promoted a "less is more" approach for PTC, to meet demands to avoid overtreatment of this generally indolent disease [3, 9–11, 18]. Particularly for low- to intermediate-risk PTC, many reports have shown that lobectomy maintained an excellent prognosis accompanying a lower rate of surgical complications [5–8, 19]. On the other hand, total thyroidectomy with RAI and TSH-suppression therapies are strongly recommended for high-risk PTC. This policy seems appropriate considering the high possibility of recurrence and mortality for high-risk PTC. However, high-quality evidence showing the superiority of this strategy in oncological outcomes over less aggressive approach remains scarce, probably because few high-risk patients in Western countries have been treated using lobectomy. Conversely, in Japan, thyroid-conserving curative surgery had been widely adopted for patients with PTC [1]. Given this unique policy, we undertook a long-term, comparative study to assess the association between extent of thyroidectomy and survival in high-risk, M0 PTC patients. As a result, lobectomy did not show significantly worse outcomes than total thyroidectomy in terms of OS, CSS or MRFS, even after propensity score matching. Moreover, extent of thyroidectomy was not an independent prognostic factor in a multivariate analysis, while older age, massive extrathyroidal invasion and large nodal metastasis were important risk factors for survival in patients with high-risk PTC. Although we did not examine molecular markers in all cases, *TERT* promoter mutation appears to represent a significant risk factor for worse outcomes, as described previously [14, 20, 21].

The study cohort was from a tertiary oncology referral center, so the patients might have had much higher-risk features, such as massive extrathyroidal invasion or large nodal metastasis, compared to other reports [12, 13]. Indeed, a total of 56 patients underwent extended radical surgery including full-layer resection of the trachea/larynx and/or esophagus/pharynx or wide dissection to the mediastinum or retropharyngeal lymph nodes. For such "super" high-risk cases, total thyroidectomy with RAI and TSH suppression therapies might be incompetent because the treatments target biologically authentic characteristics of thyroid follicular cells, including RAI avidity and TSH dependency. We speculate that more specific components of high-risk PTC would benefit from total thyroidectomy. As the CIH classification [4] uses a narrower criterion for high-risk PTC than the JAES definition, we examined the relationship between extent of thyroidectomy and CSS for patients with JAES high-risk, CIH low-risk PTC. Although the TT group showed marginally better CSS (10-year CSS, 98.5%) than the LT group (10-year CSS, 96.5%), the difference was not significant (p = 0.47). Neither younger (< 55 years) patients nor *TERT* promoter mutation-negative patients showed superiority of the TT group over the LT group in CSS (p = 0.71 and p = 0.13, respectively). Further research is needed to elucidate the definitive indications for total thyroidectomy.

In this study, no difference in the rate of permanent recurrent laryngeal nerve palsy per nerve at risk was identified between the LT group and the TT group (5.1% vs. 5.1%, for patients without preoperative recurrent laryngeal nerve palsy or resection of the nerve). However,

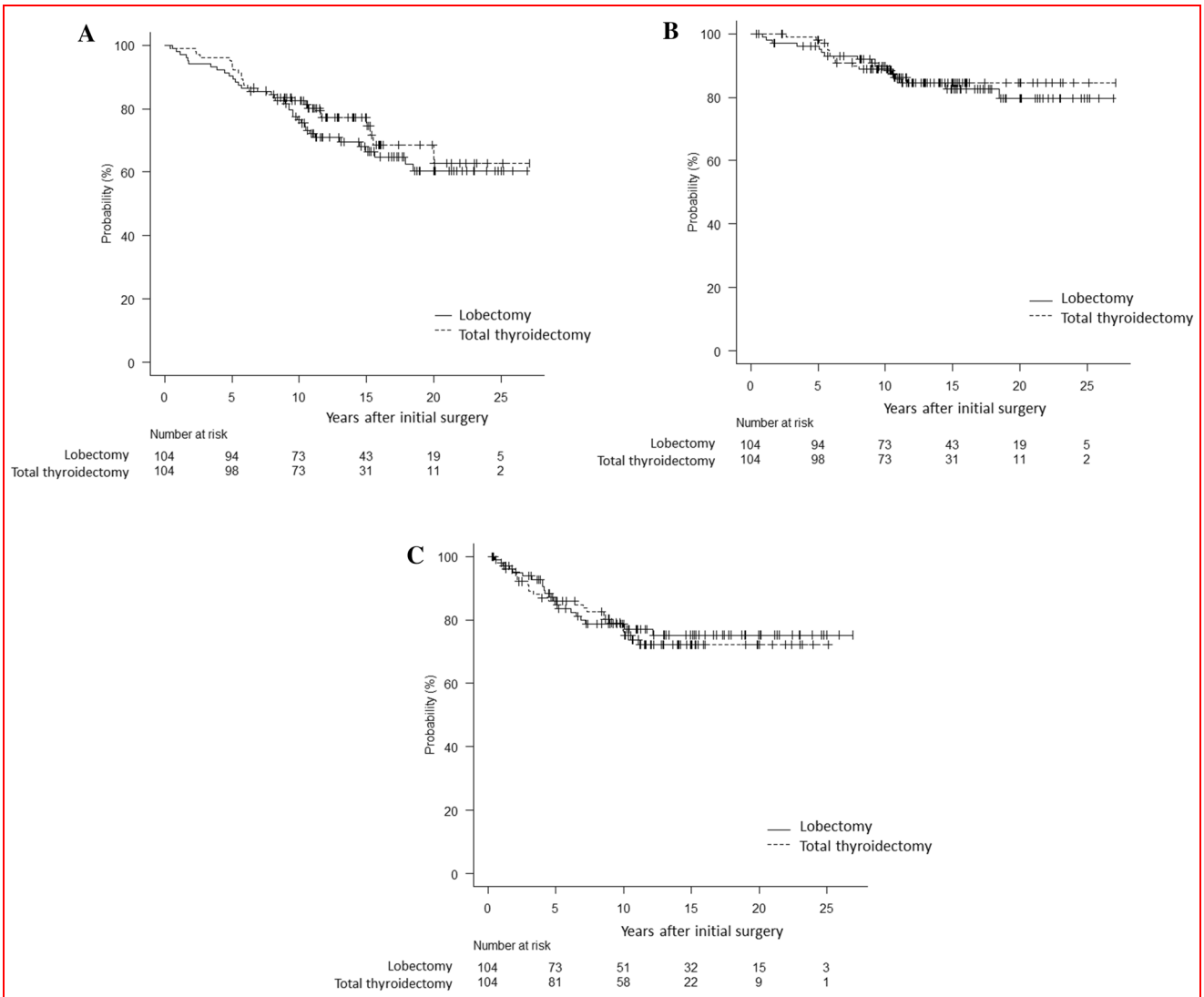

Fig. 3 Extent of thyroidectomy and treatment outcomes for high-risk PTC without initial distant metastasis, the matched cohort **a** Overall survival **b** Cause-specific survival **c** Distant recurrence-free survival PTC, papillary thyroid carcinoma

20 patients from the TT group eventually showed transient or permanent bilateral recurrent laryngeal nerve palsy necessitating tracheostoma. Patients who underwent completion thyroidectomy did not show increased complication rates. Several studies have investigated health-related quality of life (QOL) and extent of thyroidectomy in low- or intermediate-risk patients [22–25]. The results varied, but complications related to total thyroidectomy and RAI therapy might be associated with poor QOL among survivors of thyroid cancer. Comprehensive studies on patient-reported outcomes among high-risk patients are necessary, because those patients are usually older, with more comorbidities and shorter life expectancy than low-risk patients.

Meanwhile, total thyroidectomy still offers advantages in the management of high-risk PTC. In addition to static risk-classification systems, Tuttle et al. proposed dynamic risk stratification using the response to initial treatment to more accurately assess the likelihood of structural recurrence [26]. Initially, the dynamic risk stratification system was applied for patients with total thyroidectomy and RAI remnant ablation. Recent studies have shown that the system can also be used in patients with lobectomy or total thyroidectomy without RAI [27–30]. However, the predictive value of dynamic risk stratification for lobectomy is usually inferior to that for total thyroidectomy with RAI. Miyauchi et al. advocated Tg-doubling time as a valuable prognostic predictor in patients with PTC, but its utility presupposes total thyroidectomy [31].

Multi kinase inhibitors such as sorafenib and lenvatinib have recently appeared as a treatment option for thyroid cancer [32, 33]. These drugs are antiangiogenic inhibitors

Table 4 Univariate analysis of risk factors for cause-specific and distant recurrence-free survival of high-risk papillary thyroid carcinoma patients without initial distant metastasis; entire cohort

Risk factor	Number of patients	Cause-specific death	10-year CSS	*p* value[a]	Distant site recurrence	10-year MRFS	*p* value[a]
Age							
< 55 years	155	4	98.0%	< 0.0001	18	88.5%	< 0.0001
≥ 55 years	216	47	83.0%		66	64.2%	
Sex							
Male	125	16	89.8%	0.71	29	75.8%	0.91
Female	243	35	89.3%		55	74.8%	
Tumor size							
≤ 4 cm	231	28	91.6%	0.10	51	76.9%	0.43
> 4 cm	137	23	86.0%		33	72.1%	
Massive extrathyroidal invasion							
Absent	268	26	93.2%	< 0.0001	48	81.2%	< 0.0001
Present	100	25	79.2%		36	56.9%	
Multiplicity							
Absent	193	25	90.5%	0.61	38	79.0%	0.14
Present	175	26	88.3%		46	71.0%	
Large nodal metastasis ≥ 3 cm							
Absent	240	27	93.3%	0.038	49	77.2%	0.075
Present	128	24	82.3%		35	70.9%	
BRAF V600E mutation							
Negative	27	3	88.9%	0.60	4	83.7%	0.56
Positive	131	20	89.9%		29	77.2%	
TERT promoter mutation							
Negative	96	5	97.9%	< 0.0001	11	88.9%	< 0.0001
Positive	62	18	77.0%		22	58.5%	

CSS, cause-specific survival; MRFS, distant recurrence-free survival

[a] p-values were calculated using the log-rank test

Table 5 Cox proportional hazards model for cause-specific and distant recurrence-free survival of high-risk papillary thyroid carcinoma patients without initial distant metastasis

Risk factor	Cause-specific survival			Distant recurrence-free survival		
	Hazard ratio	95% confidence interval	*p* value	Hazard ratio	95% confidence interval	*p* value
Age ≥ 55 years	13.29	4.62–38.17	< 0.0001	3.56	2.06–6.15	< 0.0001
Female sex	1.25	0.69–2.27	0.46	1.08	0.69–1.71	0.73
Tumor size > 4 cm	2.34	1.32–4.17	0.0038	1.58	1.00–2.48	0.051
Massive extrathyroidal invasion	2.31	1.31–4.10	0.0040	2.14	1.34–3.42	0.0014
Large nodal metastasis ≥ 3 cm	3.34	1.87–5.99	< 0.0001	2.34	1.45–3.80	0.00056
Total thyroidectomy	1.03	0.58–1.83	0.92	1.01	0.63–1.61	0.97

and can be provided for patients with unresectable, progressive differentiated thyroid carcinoma (DTC) after verifying RAI resistance. High-risk DTC patients thus need to be treated by total thyroidectomy and RAI beforehand. At present, other mutation-specific drugs have been developed, targeting features such as *BRAF* mutation, *RET* mutation/fusion and *NTRK* fusion [34]. Genetic evaluation for each high-risk patient might lead to individualized approaches avoiding unnecessary total thyroidectomy and RAI therapy in the near future.

This study has several limitations. As a single-center, retrospective study, selection bias regarding treatment

procedures may have affected the outcomes went against more aggressive treatment including total thyroidectomy with RAI. Even though we conducted propensity score-matching, unknown confounding factors could have been present. Rather small sample size could lead to the type II error. Only about 50% of patients underwent RAI therapy after total thyroidectomy, mainly due to accessibility issues in Japan [1].

Despite these limitations, the present retrospective study provides accurate long-term follow-up data on survival for patients with high-risk, M0 PTC and curative surgery with lobectomy showed almost identical oncological outcomes to total thyroidectomy. The benefits of total thyroidectomy for high-risk PTC should be reexamined at a higher level of evidence, hopefully by randomized controlled trials.

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Author contributions Study concept, design, interpretation and writing, IS; statistical data analysis, IS and HK; acquisition of the data, IS, AE, WS, KT; methodology, investigation and validation for molecular marker analysis, KT and AE; funding acquisition, IS. All authors contributed to drafting of the manuscript and critical revisions and agreed to publication of the submitted version of the manuscript.

Declaration

Declarations

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval The institutional review board of Cancer Institute Hospital approved the study protocol (IRB number 2013–1128, 24 January 2014). All subjects gave their informed consent for inclusion before they participated in the study.

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