Surgery 165 (2019) 629–636

Contents lists available at ScienceDirect

Surgery

journal homepage: www.elsevier.com/locate/surg

Total thyroidectomy's association with survival in papillary thyroid cancers and the high proportion of total thyroidectomy in low-risk patients: Analysis of Korean nationwide data ☆

Hyun-Soo Zhang, MPH[a,b], Eun-Kyung Lee, MD, PhD[c], Yuh-Seog Jung, MD, PhD[b,c], Byung-Ho Nam, PhD[d], Kyu-Won Jung, MS[e], Hyun-Joo Kong, MS[e], Young-Joo Won, PhD[c,e], Boyoung Park, MD, PhD[a,*]

[a] Department of Medicine, College of Medicine, Hanyang University, Seoul, Korea
[b] Graduate School of Cancer Science and Policy, National Cancer Center, Goyang, Korea
[c] Center for Thyroid Cancer, Head and Neck Oncology Clinic, National Cancer Center, Goyang, Korea
[d] Herings, Institute of Advanced Clinical and Biomedical Research, Seoul, Korea
[e] National Cancer Control Institute, National Cancer Center, Goyang, Korea

ARTICLE INFO

Article history:
Accepted 28 August 2018
Available online 17 October 2018

ABSTRACT

Background: Papillary thyroid cancer has an excellent prognosis, but the appropriate level of treatment is controversial. We compared survival between total thyroidectomy and less-than-total thyroidectomy, and examined the proportion of patients with papillary thyroid cancer in Korea undergoing total thyroidectomy.

Methods: A nationwide sample of 5,230 papillary thyroid cancer patients was included (total thyroidectomy: 4,262, less-than-total thyroidectomy: 968). Using multivariate Cox regression, we compared overall survival and cause-specific survival by the extent of thyroidectomy (total thyroidectomy versus less-than-total thyroidectomy) for a 1:1 optimal match via the propensity score and for the total study population. We also compared overall survival by extent of thyroidectomy and the proportion of total thyroidectomy in different risk groups using papillary thyroid cancer staging systems.

Results: We saw no difference in overall survival by extent of thyroidectomy in the propensity score matched population and the total study population (hazard ratio for less-than-total thyroidectomy 0.82, 95% confidence interval 0.52–1.29; hazard ratio for less-than-total thyroidectomy 1.03, 95% confidence interval 0.71–1.48, respectively). Similarly, there were no differences in thyroid cancer–specific survival by extent of thyroidectomy. None of the different risk groups showed differences in overall survival by surgical extent, although total thyroidectomy improved overall survival in older females with larger tumors. The proportion of papillary thyroid cancer patients who received a total thyroidectomy was 80% or greater regardless of risk group classification.

Conclusion: Total thyroidectomy had no survival advantage over less-than-total thyroidectomy in Korean papillary thyroid cancer patients except in a specific high-risk group. 80% or more of low-risk papillary thyroid cancer patients received a total thyroidectomy. These results suggest that further patient-centered treatment which considers both quality of life and clinical outcome is needed.

Introduction

Thyroid cancer incidence increased rapidly during the past few decades worldwide.[1,2] This increase is mostly attributed to an increase in small papillary thyroid cancers (PTCs) and in this regard, the stability of mortality secondary to thyroid cancer strongly suggests overdiagnosis.[1,3] This situation is especially important in South Korea because the incidence of thyroid cancer increased by 24.2% per year from 1999 to 2010, and the proportion of small (<1 cm) PTCs among all thyroid cancers increased from 17.6% in 1999 to 58.7% in 2008.[4–6]

Current treatment options for PTC are total removal (total or near-total thyroidectomy) or partial removal (lobectomy or subtotal thyroidectomy), and active surveillance without operative interven-

☆ Supported by a research fund from Hanyang University, Seoul, Korea (Research No. HY-201800000000615).

* Corresponding author: Associate Professor, Department of Medicine, College of Medicine, Hanyang University, 222 Wangsimni-ro, Seongdong-gu, Seoul, 04763, Korea.

E-mail address: hayejine@hanmail.net (B. Park).

https://doi.org/10.1016/j.surg.2018.08.030
0039-6060/

tion is also being considered a viable option.[1] The 2006 guidelines of the American Thyroid Association (ATA) had recommended total removal as initial treatment for most patients with thyroid cancer, because total removal may decrease the chance of disease recurrence.[7] However, a total thyroidectomy (TT) involves a greater risk of operative complications compared with a less-than-total thyroidectomy (LTT) and requires lifelong thyroid replacement therapy. The ATA changed its treatment recommendations from "(total) thyroidectomy is recommended for all patients with PTC measuring > 1 cm" in the 2009 ATA guidelines[8] to "(total) thyroidectomy or lobectomy can be used in properly selected patients with PTCs measuring 1∼4 cm"[9] in the 2015 ATA guidelines.

Some previous studies compared PTC survival by different extents of thyroidectomy.[10–14] Results have been inconsistent, with some reporting decreased recurrence and increased survival outcomes for TT compared with thyroid lobectomy,[10] and others rebutting this conclusion.[11,12] Studies in Korea thus far mainly reported no statistically significant difference in survival between TT and thyroid lobectomy.[13,14] To the best of our knowledge, all previous Korean studies concerning survival by the extent of thyroidectomy were from single institutions, with limited generalizability of results and more focus on recurrence-related measures. Considering that the final outcome of cancer treatment is ultimately patient survival, a broader nationwide study focusing on survival by the extent of thyroidectomy can help identify the better treatment option at the population level.

Hence, using nationally representative, multicenter data from Korea, we compared PTC patients' survival between TT and LTT to answer whether a survival difference exists between the two operative treatments. We utilized matching to increase comparability between treatment groups and examined survival by extent of thyroidectomy in the unmatched total study population as well. We also examined survival by extent of thyroidectomy and the proportion of patients who received a TT in different risk groups, defined by PTC staging systems.

Methods

Study population

The Korea Central Cancer Registry (KCCR) conducted the National Epidemiologic Survey of Thyroid cancer (NEST) in 2011 to facilitate research on causes for the recent rapid increase in thyroid cancers in Korea and to develop subsequent health policies.[5] The KCCR NEST is composed of a nationally representative sample of patients with thyroid cancer diagnosed in 1999, 2005, and 2008. The first year, 1999, was selected as the starting point of the large increase in the incidence of thyroid cancer in Korea, and the year 2005 was sampled as a midway point between 1999 and 2008, with thyroid cancer becoming the most frequent cancer among Korean women since 2005. The NEST used a two-stage sampling procedure, where stage one extracted 24 hospitals stratified by region among 300 Korean hospitals throughout the nation, and stage two performed probability-proportional-to-size sampling of patients among those 24 hospitals, to which all participants provided informed consent. The NEST has information regarding demographics, medical history, smoking and drinking history, other diseases or diagnoses, staging and pathologic information, and treatment information. The NEST also tracked the date and cause of death for the deceased through mortality statistics from Statistics Korea.[4]

The current study population was restricted to patients with PTC in whom treatment information was available (N = 5,230). We dichotomously grouped the study population according to extent of thyroidectomy into TT (N = 4,262) or LTT (N = 968), where LTT was defined as operations that were neither total nor near-total thyroidectomies, including thyroid lobectomy (N = 698, 72.1%), subtotal thyroidectomy (N = 107, 11.0%), partial thyroidectomy (N = 81, 8.4%), and others (N = 82, 8.5%). The process for selection of the study population is outlined in Fig. 1. We selected as covariates age at diagnosis; sex; tumor size; method of detection; lymph node metastasis (LNM); extra-thyroidal extension (ETE); multifocality; smoking history; drinking history; comorbidities defined as any chronic disease diagnosed by a physician through chart review; other thyroid diagnoses, such as Hashimoto's disease; a family history of thyroid cancer; presence of other cancers; and distant metastases, to adjust for confounding of treatment selection and also to calculate the propensity score for matching. These variables were chosen based on previous studies of the risk factors and staging systems for PTC.[1,5,15] Missing data for all variables were dummy-coded as "unknown" to prevent the exclusion of patients without complete variable records. Survival outcome was defined as the time-to-event, where the event indicates patient death, and the study endpoints were overall survival (OS), where the event indicates patient death attributable to any cause; thyroid cancer-specific survival, where the event indicates patient death attributable to thyroid cancer; other cancer-specific survival, where the event indicates patient death attributable to cancer other than thyroid cancer; and other causes-specific survival, where the event indicates patient death attributable to a cause other than cancer. Survival status was followed up until December 31, 2015, with a median follow-up at 122 months (range 1–207 months). The study protocol was approved by the Institutional Review Board of Korea's National Cancer Center (Goyang, Korea).

Statistical analysis

We utilized matching to replicate a randomized trial as closely as possible for an unbiased estimate of association between the extent of thyroidectomy and PTC survival. We compared various matches by different distance measures, matching methods, and matching ratios to select the best match for a causal effect estimation.[16,17] To choose the best match, we considered the standardized mean difference, variance ratio difference, and statistical power.[18] The matching methods considered and the best match chosen are provided as Supplementary data.

We also classified our study population into low-, intermediate-, and high-risk groups, using PTC staging systems.[15,19] Among seven staging systems that were applicable to the current study, tumor, node, metastasis (TNM) staging 6th edition; European Organisation for Research and Treatment of Cancer (EORTC) staging; grade, age, metastases, extent, size (GAMES) staging; and Noguchi Thyroid Clinic staging were chosen for further analysis. The criterion for selection was the proportion of variation explained, a generalized R^2 measure, which quantifies the prognostic accuracy of the staging system in terms of the system's degree of association with survival time.[15] Although the metastasis, patient age, completeness of resection, local invasion, and tumor size (MACIS) staging system is known to perform well in classification of PTC risk,[15,19] this system was excluded because of an unavailable staging component (complete resection) in the current study.

Continuous variables, including age and tumor size, were categorized in the current study, and all baseline characteristics were presented with frequencies and percentages (N [%]). We used χ^2 tests to detect differences in categorical variables between TT and LTT groups. Survival curves were plotted using the Kaplan-Meier method, and equivalence of curves was determined using the log-rank test. The Cox proportional hazards regression with hazard ratios (HR) and corresponding 95% confidence intervals (CI) were used to assess the difference in survival by the extent of thyroidectomy, and the proportional hazards assumption was tested for all variables included in the multivariate regres-

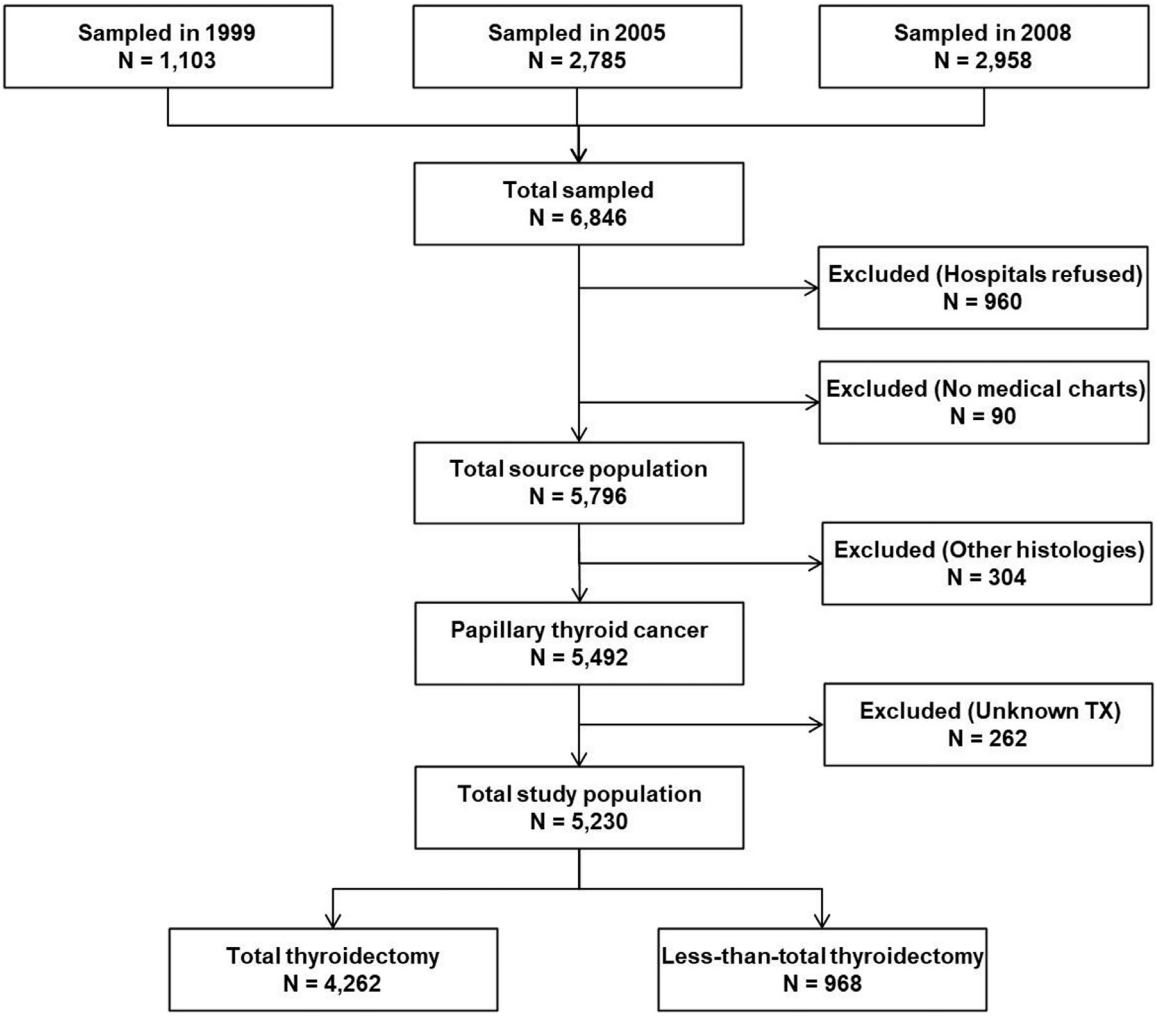

Fig 1. The selection flowchart of the study population of Korean patients with papillary thyroid cancer (PTC) in the Korea Central Cancer Registry's National Epidemiologic Survey of Thyroid cancer (KCCR-NEST), sampled in 1999, 2005, and 2008. *TX*, extent of thyroidectomy.

sion model. Variables that violated this assumption were stratified by their respective categories, and regression coefficients were estimated via maximizing the likelihood function formulated by multiplying partial likelihood functions of each category. For comparability across various survival endpoints, the clinically relevant variables of age, sex, tumor size, LNM, ETE, multifocality, and the presence of other cancers were adjusted for in multivariate analyses. These variables were selected based on the association with PTC survival in previous studies and statistical significance in the current study.[10,12–15,19] All reported *P* values were two-sided. We used SAS 9.4 and SAS/STAT 14.2 (SAS Institute, Cary, NC) for all statistical analyses.

Results

Table 1 presents the baseline characteristics of the total study population and the 1:1 optimal match via the propensity score (the PSM population) by the extent of thyroidectomy. For the total study population, proportions of age at diagnosis, tumor size, LNM, ETE, and multifocality by their respective categories were especially different between the TT and LTT groups, with the TT group being older, having larger tumors, more LNM, more ETE, and more multifocal tumors. All PTC patients who had distant metastases received a TT in the current study (N = 9). For the PSM population, none of the variables showed statistically significant differences in χ^2 tests between the two treatment groups. No patients with distant metastasis were included in the PSM population. Table 1 also presents frequencies and proportions of various types of survival events (overall, thyroid cancer-specific, other cancer-specific, and other causes-specific events) by the extent of thyroidectomy in the total study population and the PSM population. Proportions of each event by the extent of thyroidectomy were similar between the two populations.

Table 2 displays the effect of the extent of thyroidectomy on overall and cause-specific survival (OS and CSS), with unadjusted and adjusted HRs in the total study population and PSM population. No statistically significant differences in OS and CSS existed between patients who received a TT or an LTT in the total study population and PSM population. The HRs for LTT versus TT for survival endpoints OS, thyroid cancer-specific survival, other cancer-specific survival, and other causes-specific survival were 1.03 (95% CI 0.71–1.48), 1.08 (95% CI 0.53–2.23), 1.13 (95% CI 0.64–2.00), and 0.87 (95% CI 0.46–1.66) in the total study population, and 0.82 (95% CI 0.52–1.29), 1.10 (95% CI 0.42–2.85), 0.76 (95% CI 0.38–1.52), and 0.96 (95% CI 0.43–2.13) in the PSM population.

Table 3 shows OS by the extent of thyroidectomy for various risk groups (low, intermediate, or high risk) in the total study population, using the TNM, EORTC, GAMES, and Noguchi staging system. TNM stages I and II, and EORTC stages IV and V were combined because of the small number of TNM stage II (N = 30) and

Table 1
Baseline characteristics of the total study population and the 1:1 optimal match via the propensity score (PSM population) for Korean patients with papillary thyroid cancer (PTC) sampled in 1999, 2005, and 2008.

Variables	Total study population: Extent of thyroidectomy			PSM population: Extent of thyroidectomy		
	LTT group (N=968)	TT group (N=4,262)	*P* value	LTT group (N=968)	TT group (N=968)	*P* value
Age at diagnosis			.011			.460
<35	188 (19.4)	792 (18.6)		188 (19.4)	201 (20.8)	
35~45	311 (32.1)	1,185 (27.8)		311 (32.1)	323 (33.4)	
45~55	280 (28.9)	1,288 (30.2)		280 (28.9)	281 (29.0)	
>55	189 (19.5)	997 (23.4)		189 (19.5)	163 (16.8)	
Tumor size			<.001			.854
<1.0 cm	679 (70.2)	2,255 (52.9)		679 (70.2)	671 (69.3)	
1.0~2.0 cm	151 (15.6)	1,302 (30.6)		151 (15.6)	164 (16.9)	
>2.0 cm	101 (10.4)	577 (13.5)		101 (10.4)	95 (9.8)	
Unknown	37 (3.8)	128 (3.0)		37 (3.8)	38 (3.9)	
Sex			.210			1.000
Male	132 (13.6)	649 (15.2)		132 (13.6)	132 (13.6)	
Female	836 (86.4)	3,613 (84.8)		836 (86.4)	836 (86.4)	
Method of detection			.018			.394
Screening	422 (43.6)	2,066 (48.5)		422 (43.6)	401 (41.4)	
Clinical	306 (31.6)	1,265 (29.7)		306 (31.6)	334 (34.5)	
Unspecified	240 (24.8)	931 (21.8)		240 (24.8)	233 (24.1)	
Lymph node metastasis (LNM)			<.001			.737
No	448 (46.3)	1,832 (43.0)		448 (46.3)	436 (45.0)	
Yes	183 (18.9)	1,759 (41.3)		183 (18.9)	196 (20.3)	
Unknown	337 (34.8)	671 (15.7)		337 (34.8)	336 (34.7)	
Extra-thyroidal extension (ETE)			<.001			.958
No	599 (61.9)	1,946 (45.7)		599 (61.9)	599 (61.9)	
Yes	308 (31.8)	2,162 (50.7)		308 (31.8)	305 (31.5)	
Unknown	61 (6.3)	154 (3.6)		61 (6.3)	64 (6.6)	
Multifocality			<.001			.895
Unifocal	791 (81.7)	2,709 (63.6)		791 (81.7)	783 (80.9)	
Multifocal	145 (15.0)	1,454 (34.1)		145 (15.0)	152 (15.7)	
Unknown	32 (3.3)	99 (2.3)		32 (3.3)	33 (3.4)	
Distant metastasis			.076			.219
No	915 (94.5)	4075 (95.6)		915 (94.5)	902 (93.2)	
Yes	0 (0.0)	9 (0.2)		0 (0.0)	0 (0.0)	
Unknown	53 (5.5)	178 (4.2)		53 (5.5)	66 (6.8)	
Smoking history			.005			.949
Ever smoked	67 (6.9)	237 (5.6)		67 (6.9)	66 (6.8)	
Never smoked	678 (70.1)	3,200 (75.1)		678 (70.1)	673 (69.5)	
Unknown	223 (23.0)	825 (19.3)		223 (23.0)	229 (23.7)	
Drinking history			.037			.663
Drinker	127 (13.0)	568 (13.3)		127 (13.0)	114 (11.8)	
Nondrinker	624 (63.8)	2,892 (67.9)		624 (63.8)	631 (65.2)	
Unknown	217 (23.2)	802 (18.8)		217 (23.2)	223 (23.0)	
Comorbidity			.288			.752
No	725 (74.9)	3,121 (73.2)		725 (74.9)	731 (75.5)	
Yes	243 (25.1)	1,141 (26.8)		243 (25.1)	237 (24.5)	
Other diagnosis			.001			.883
None	590 (60.9)	2,347 (55.1)		590 (60.9)	607 (62.7)	
Hashimoto's disease	168 (17.4)	940 (22.0)		168 (17.4)	159 (16.4)	
Other	205 (21.2)	928 (21.8)		205 (21.2)	197 (20.4)	
Unknown	5 (0.5)	47 (1.1)		5 (0.5)	5 (0.5)	
Family history of thyroid cancer			.131			.538
No	761 (78.6)	3433 (80.5)		761 (78.6)	744 (76.9)	
Yes	28 (2.9)	147 (3.5)		28 (2.9)	35 (3.6)	
Unknown	179 (18.5)	682 (16.0)		179 (18.5)	189 (19.5)	
Presence of other cancers			.262			.437
No	800 (82.6)	3,502 (82.2)		800 (82.6)	795 (82.1)	
Yes	35 (3.6)	204 (4.8)		35 (3.6)	27 (2.8)	
Unknown	133 (13.7)	556 (13.0)		133 (13.7)	146 (15.1)	
Events*			.956			.924
Overall	**38 (100)**	**169 (100)**		**38 (100)**	**40 (100)**	
Thyroid cancer-specific	10 (26.3)	45 (26.6)		10 (26.3)	9 (22.5)	
Other cancer-specific	16 (42.1)	67 (39.6)		16 (42.1)	18 (45.0)	
Other causes-specific	12 (31.6)	57 (33.7)		12 (31.6)	13 (32.5)	

* Overall event, death owing to any cause; Thyroid cancer–specific event, death attributable to thyroid cancer; Other cancer-specific event, death attributable to cancer other than thyroid cancer; Other causes–specific event, death attributable to a cause other than cancer.

EORTC stage V (N = 7) patients in the current study. EORTC stages I and II were also combined because of the estimated HR of LTT versus TT being zero, with no events in the LTT group among EORTC stage I patients (N = 832). TNM and EORTC stages I and II were considered low risk, TNM and EORTC stage III were considered intermediate risk, and TNM stage IV and EORTC stages IV and V were considered high risk. CSS by the extent of thyroidectomy in various risk groups were not examined because of the small number of events in each risk group. For TNM staging, there were 1,005 patients (19.2%) classified as unknown risk,

Table 2
PTC survival by the extent of thyroidectomy (LTT versus TT) in the total study population and the 1:1 optimal match via the prepensity score (PSM population) for Korean PTC patients sampled in 1999, 2005, and 2008.

Survival end point	Total study population				PSM population			
	Unadjusted		Adjusted*		Unadjusted		Adjusted	
	HR (95% CI)†	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Overall survival	0.93 (0.66–1.33)	.706	1.03 (0.71–1.48)	.883	0.96 (0.61–1.49)	.838	0.82 (0.52–1.29)	.391
Thyroid cancer-specific survival	0.77 (0.43–1.40)	.397	1.08 (0.53–2.23)	.829	1.11 (0.45–2.74)	.814	1.10 (0.42–2.85)	.850
Other cancer-specific survival	0.92 (0.54–1.57)	.771	1.13 (0.64–2.00)	.683	0.89 (0.45–1.75)	.734	0.76 (0.38–1.52)	.440
Other causes-specific survival	0.91 (0.52–1.60)	.745	0.87 (0.46–1.66)	.674	0.93 (0.43–2.05)	.866	0.96 (0.43–2.13)	.912

* All adjusted for age, sex, tumor size, lymph node metastasis (LNM), extra-thyroidal extension (ETE), multifocality, and presence of other cancers.
† All hazard ratios (HR) are for less-than-total thyroidectomy (LTT), with total thyroidectomy (TT) as reference.

Table 3
Frequency and proportion of overall events (all-cause deaths), frequency and proportion of TT, and PTC OS by the extent of thyroidectomy (LTT versus TT) in the total study population for different risk groups by various PTC staging systems among Korean PTC patients sampled in 1999, 2005, and 2008.

Staging system	Risk group	N	Overall events (%)‡	TT (%)†	Unadjusted		Adjusted*	
					HR (95% CI)§	*P* value	HR (95% CI)	*P* value
TNM	I & II¶	2,896	48 (1.6)	2,311 (79.8)	1.39 (0.74–2.64)	.309	1.24 (0.64–2.41)	.521
	III	998	47 (4.7)	868 (86.9)	0.90 (0.38–2.13)	.815	1.05 (0.44–2.52)	.907
	IV	331	37 (11.2)	308 (93.1)	1.85 (0.72–4.76)	.202	1.06 (0.37–3.06)	.910
EORTC	I & II¶	2,811	30 (1.1)	2,238 (79.6)	1.15 (0.50–2.69)	.740	0.76 (0.32–1.85)	.552
	III	1,675	69 (4.1)	1,424 (85.0)	1.05 (0.55–2.00)	.889	0.96 (0.49–1.86)	.901
	IV & V¶	397	81 (20.4)	344 (86.6)	1.39 (0.79–2.44)	.247	1.26 (0.68–2.33)	.466
GAMES	Low	2,113	16 (0.8)	1,693 (80.1)	1.26 (0.40–3.90)	.695	0.95 (0.28–3.21)	.929
	Intermediate	2,722	143 (5.3)	2,260 (83.0)	1.10 (0.72–1.67)	.660	1.23 (0.79–1.89)	.361
	High	102	24 (23.5)	83 (81.4)	0.63 (0.19–2.13)	.461	0.53 (0.11–2.51)	.421
Noguchi	Low	3,641	46 (1.3)	2,937 (80.7)	1.09 (0.54–2.20)	.807	1.05 (0.48–2.31)	.895
	Intermediate	889	83 (9.3)	763 (85.8)	1.16 (0.66–2.03)	.612	1.06 (0.59–1.90)	.850
	High	330	41 (12.4)	302 (91.5)	2.06 (0.91–4.65)	.083	1.75 (0.41–7.47)	.453

* All adjusted for age, sex, tumor size, lymph node metastasis (LNM), extra-thyroidal extension (ETE), multifocality, and presence of other cancers.
† Proportion of total thyroidectomy (TT) = frequency of total thyroidectomy (TT) / N × 100 in each risk group.
‡ Proportion of overall events = frequency of overall events / N × 100 in each risk group.
§ All hazard ratios (HR) are for less than total thyroidectomy (LTT), with total thyroidectomy (TT) as reference.
¶ TNM stages I and II and EORTC stages IV and V were combined because of the small number of TNM stage II (N = 30) and EORTC stage V (N = 7) patients in the current study. EORTC stages I and II were combined because of the estimated HR being 0, with no events in the LTT group among EORTC stage I patients.
EORTC, European Organization for Research and Treatment of Cancer; *GAMES*, grade, age, metastases, extent, size; *Noguchi*, Noguchi Thyroid Clinic; *TNM*, tumor, node, metastasis.

mainly because of the large proportion of patients with unknown LNM status (19.3%, Table 1). No differences in OS by the extent of thyroidectomy existed in TNM risk groups, and all adjusted HRs and *P* values were insignificant. In high-risk groups via EORTC and Noguchi staging, HRs for LTT versus TT were greater than 1, suggesting a greater hazard of all-cause death for LTT compared with TT, but were not statistically significant. In contrast, the high-risk group via GAMES staging showed an LTT versus TT HR that was much less than one (0.53), despite statistical insignificance. There was no significant interaction between the extent of thyroidectomy and risk group in any staging system, and overall, none of the risk groups showed statistically significant differences in OS by the extent of thyroidectomy. Fig. 2 displays Kaplan-Meier survival curves by the extent of thyroidectomy among PTC low-risk groups. Survival curves by the extent of thyroidectomy for all four staging systems crossed over multiple times, visually confirming the insignificant difference in OS by the extent of thyroidectomy among low-risk groups. In addition, we examined OS by the extent of thyroidectomy among subgroups of all variables included in multivariate adjustment (age, tumor size, sex, LNM, ETE, multifocality, and presence of other cancers) to evaluate any heterogeneity in OS by the extent of thyroidectomy, which is provided as Supplementary data.

Table 3 also displays the frequency and proportion of overall events (i.e. all-cause deaths) and the frequency and proportion of patients who received a TT by risk group and staging system. Compared with the large difference in the proportion of overall events among low-, intermediate-, and high-risk groups, the proportion of patients who received a TT were largely similar across risk groups for all staging systems. In low-risk groups, approximately 80% of patients received a TT, whereas the proportion of patients who experienced an event was 0.8∼1.6%. In high-risk groups, the proportion of TT was 81∼93% and the proportion of events was 11∼24%. The proportion of TT in the total study population (N = 5,230) was 81.5%, and the proportion of TT increased from 77.7% in 1999 to 81.6% in 2005, and 82.5% in 2008.

Discussion

In the current study, we investigated the effect of the extent of thyroidectomy (TT or LTT) on PTC survival among Korean patients, using nationally representative data. The effect of the extent of thyroidectomy on OS and CSS was not statistically significant in both the total study population and the PSM population. In addition, OS by the extent of thyroidectomy was not statistically significantly different in low-, intermediate-, or high-risk groups for the total study population, as classified by the TNM, EORTC, GAMES, and Noguchi staging systems. Although the proportion of overall events (i.e. all-cause deaths) was largely different among risk groups in each staging system, the proportion of patients who received a TT was 80% or greater in all risk groups.

A previous study used multivariate adjustment to assess PTC outcomes by the extent of thyroidectomy, and demonstrated that TT improved recurrence and survival outcomes of PTC patients

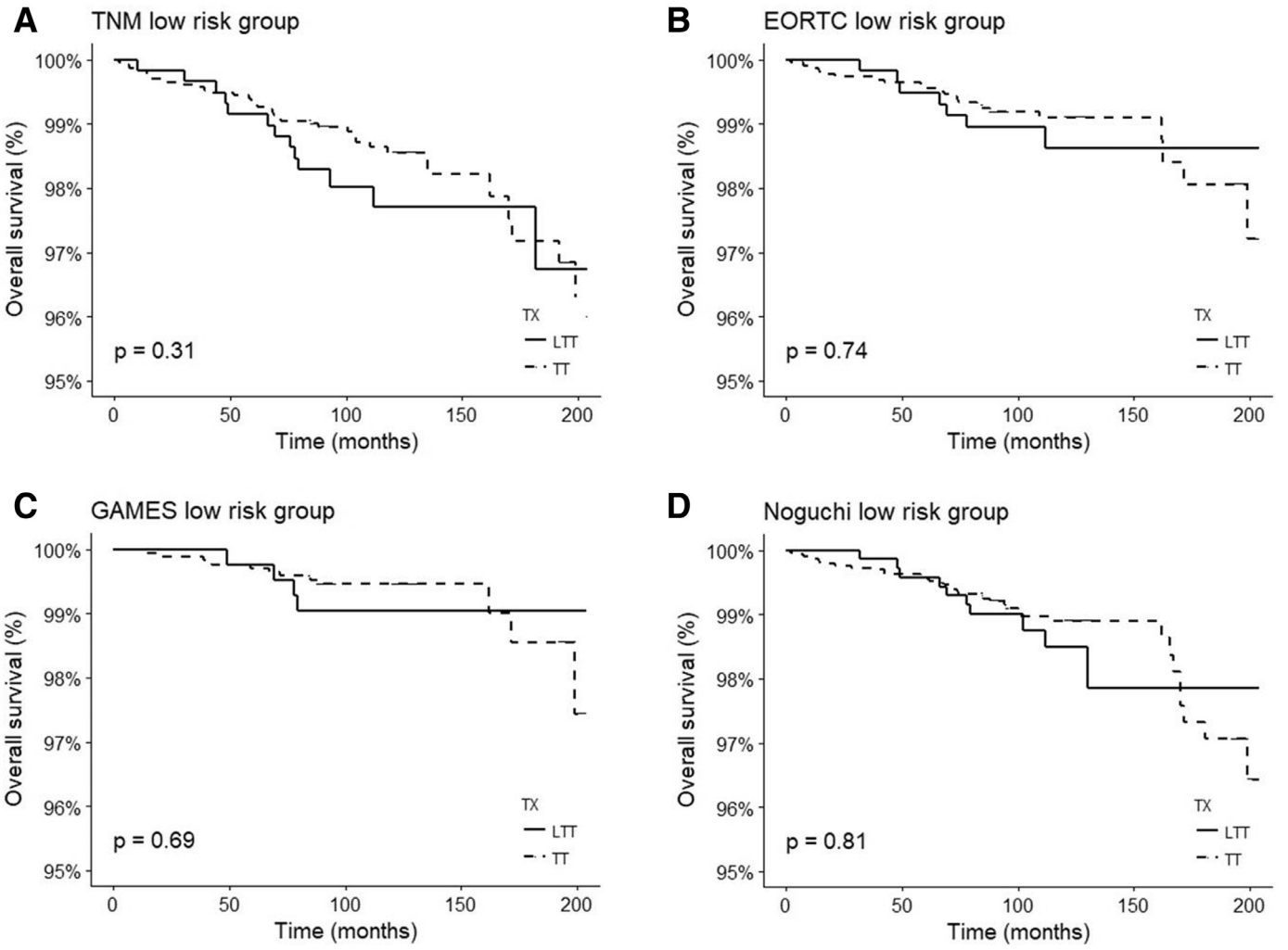

Fig 2. Kaplan-Meier survival curves by the extent of thyroidectomy (TX), comparing overall survival between total thyroidectomy (TT) and less-than-total thyroidectomy (LTT) groups in the total study population for Korean papillary thyroid cancer (PTC) low-risk groups defined by (*A*) TNM, (*B*) EORTC, (*C*) GAMES, and (*D*) Noguchi staging systems, sampled in 1999, 2005, and 2008. *EORTC*, European Organization for Research and Treatment of Cancer; *GAMES*, grade, age, metastases, extent, size; *Noguchi*, Noguchi Thyroid Clinic; *TNM*, tumor, node, metastasis.

with tumor size ≥1 cm compared with thyroid lobectomy.[10] However, potential confounders in treatment selection (the extent of thyroidectomy), such as ETE and multifocality, were not adjusted for in this study. Failing to adjust for unavailable or unknown confounders is a well-known limitation of multivariate adjustment, and other studies employed matching for a fairer comparison between treatment groups.[13,14] Among these studies, Lee et al[13] utilized 1:1 propensity score matching and reported no significant difference in OS by the extent of thyroidectomy in patients with papillary thyroid microcarcinoma, which was in agreement with the current study. We performed various types of matching to select a best match with the least selection bias. We also compared results obtained from the matched population with those obtained from multivariate adjustment only; that is, OS and CSS by the extent of thyroidectomy were compared between the PSM population with doubly robust adjustment and the total study population with multivariate adjustment only. The different directions in adjusted HRs between the two populations indicate that some residual confounding in the total study population may have been additionally matched and adjusted for in the PSM population.

Another study[20] evaluated OS by the extent of thyroidectomy in low- or high-risk groups, using the AMES staging system, similar to the analysis of our current study of various risk groups. This study reported that the extent of thyroidectomy did not affect OS in high-risk PTC. In fact, TT showed a 1.73 times greater risk of death compared with partial thyroidectomy in low-risk PTC patients, which the authors attribute to unmeasured and thus unadjusted selection bias. Other studies also support a less extensive thyroidectomy for low risk PTC patients. Nixon et al[21] stated that the extent of thyroidectomy was not an independent predictor of OS in low risk, pT1T2 N0 well-differentiated thyroid cancers, and Ebina et al[22] similarly reported no significant difference in cause-specific or disease-free survival between TT and LTT in low-risk PTCs defined by their own classification system, which was age <50 years, LNM <3 cm, minimal or no ETE, and no distant metastasis.

In the current study, an equally high proportion of TT was observed regardless of risk group classification by various PTC staging systems (around 80% regardless of risk). In contrast, the proportion of TT among low-risk patients was 59% in the study by Nixon et al[21] and only 18% in the study by Ebina et al.[22] Because active surveillance without operative intervention is being considered a viable treatment option for low-risk PTCs,[23,24] the fact that 80% or more low-risk PTC patients received a TT is concerning. We also examined the proportion of TT in a more strictly defined low-risk group, following the 2006 ATA recommendations on lobectomy only for small, isolated, intrathyroidal PTCs without cervical lymph node metastases,[7] which may have been the standard

of care during the KCCR-NEST data sampling period (1999∼2008). TT was conducted in 70% (491/701) of small (<1 cm), unifocal, intrathyroidal, node-negative PTCs in the KCCR-NEST. Even from a recurrence perspective, the 70% proportion of TT may be excessive, because small (<1 cm), unifocal, intrathyroidal (no ETE), node-negative (N0) PTCs have very low risk of recurrence, according to several recurrence risk stratification systems.[25] A reason behind the high proportion of TT in Korea for low-risk patients may be the 2006 ATA guidelines' endorsement of TT for reducing recurrences,[7] and another reason may be the falsely held belief that radioactive iodine (RAI) ablation after a TT decreases recurrence, even in low-risk patients.[1] In addition, a Korean study comparing the treatment preferences of endocrine surgeons for well-differentiated thyroid cancer (WDTC) among Korea, Japan, and the International Association of Endocrine Surgeons showed that Korean surgeons generally favored more aggressive treatment of WDTC than did surgeons in other nations. For example, 97.5% of Korean surgeons preferred a TT in 1.0 to 2.0 cm tumors compared with only 5% of Japanese surgeons, and 86% of American surgeons.[26]

The postoperative complication rate is greater in TT compared with lobectomy, which applies to high-volume and low-volume surgeons alike (14.5% versus 7.6% in high-volume surgeons, and 24.1% versus 11.8% in low-volume surgeons).[27] In addition to potential operative complications, such as permanent hypoparathyroidism, recurrent laryngeal nerve injury, and vocal cord dysfunction,[27,28] TT requires lifelong thyroid hormone replacement, which may pose a burden throughout the patient's life.[3] LTT (including lobectomy), however, has less complications and preserves thyroid function with a lesser need for hormone replacement,[1] and thus may be an excellent treatment alternative for select low-risk patients. The appropriate level of PTC treatment has been controversial,[1–3,9] and the current study adds to existing knowledge that no OS or CSS differences by the extent of thyroidectomy were observed among Korean PTC patients at the population level, further justifying the use of LTT in low-risk PTCs. Even in high-risk PTCs, no statistically significant survival benefit was observed, although some point estimates showed decreased mortality risk in TT patients.

To investigate which patient groups require a TT in terms of mortality risk, we also examined subgroups with multiple high-risk features (results not presented). High-risk features were defined as PTC prognostic factors for survival and recurrence, including older age, male sex, larger tumors, LNM, ETE, multifocality, and distant metastasis.[15,29,30] Resultantly, older (>55 years) females with larger tumors (>2 cm) who received a TT had better OS than their LTT counterparts in multivariate analysis (LTT versus TT HR 2.60, 95% CI 1.06–6.40). Other subgroups with multiple high-risk features, such as larger tumors (>2 cm) with gross ETE (T4), showed point estimates that indicated better OS in TT patients, but the results were not statistically significant. Larger studies with greater follow-up may be needed to further identify those who would benefit from a TT. Although not identified in our study, other well-known high-risk features, including tumor size >4 cm, extensive LNM (N1b), gross ETE (T4), or distant metastasis (M1) at diagnosis, also necessitate more aggressive treatment.[9,29,30]

Our study suggests that PTC treatment in Korea needs to be more evidence based and individualized, rather than taking a one-size-fits-all approach of aggressive operative treatment. Evidence-based management utilizing prognostic factors and risk groups has been proposed previously,[21,22,29] and the general guideline is LTT (lobectomy) for low-risk patients, the extent of thyroidectomy determined by individual risk assessment for intermediate-risk patients, and TT with RAI therapy for high-risk patients.[29] In addition, active surveillance trials of low-risk PTCs are continuously demonstrating watchful waiting to be as effective as immediate operative intervention,[1,23,24] and the 2015 guidelines of the ATA allow either a TT or LTT in intermediate-risk PTCs (1.0–4.0 cm, intrathyroidal, node-negative tumors).[9] Therefore, the latest evidence suggests more widely applicable patient-centered management in low- and intermediate-risk patients, where patients are empowered to make informed decisions regarding their treatment. As a requirement, patients should understand their individualized risk based on clinicopathologic factors and have adequate knowledge of the pros and cons of each treatment before ultimately choosing between lifelong thyroid replacement after TT versus follow-up of remaining tissue after LTT. When given the choice, a high percentage of eligible patients chose LTT.[22] This is contrary to the high proportion of TT across all risk groups in Korean PTC patients, suggesting unmet needs in shared decision-making between the patient and physician.

Regarding the new operative recommendations of the ATA in 2015, the ATA Guidelines task force expects improved surgical outcome and quality of life, such as decreases in operative hypoparathyroidism, laryngeal nerve damage, and need for hormone therapy in low-risk PTC patients.[31] Recent responses in Korea seem to be a promising turnaround from overdiagnosis and an unnecessarily aggressive extent of thyroidectomy for low-risk PTCs, such as the Korean Thyroid Association's statement that they flexibly accept the ATA's recommendations,[32] and further positive changes may take place as the revised ATA guidelines become more widely implemented. In addition, there has been a 35% decrease in thyroid cancer operations in Korea, comparing the two periods before and after the physician coalition call to stop unnecessary thyroid cancer screening in March 2014.[33] A follow-up study regarding the treatment preferences of Korean surgeons for WDTC also reported changing trends toward a more conservative approach.[34] However, responses from Korean women in a nationwide cross-sectional survey showed that the majority of subjects (74%) still intended to undergo thyroid cancer screening regardless of overdiagnosis, indicating the need to further communicate the harms of excessive screening.[35] The high proportion of TT (70%) among small (<1 cm), unifocal, intrathyroidal, node-negative PTCs in our study is also noteworthy, and a public consensus toward less extensive treatment for these very low-risk patients that considers long-term quality of life as well as immediate clinical outcome is needed.

This study has some strengths and limitations. In comparison with earlier Korean studies, we utilized multicenter, nationwide data representative of the total Korean population. We also selected a best match, using multiple diagnostic measures to replicate a randomized trial as closely as possible, and examined OS by the extent of thyroidectomy separately in various risk groups. It should be noted, however, that no information on recurrence was included in the KCCR-NEST, and we were unable to compare recurrence by the extent of thyroidectomy. Data on histologic subtypes (e.g. tall cell, columnar cell, etc) and molecular markers (e.g. BRAF, TERT, etc) were also unavailable in the KCCR-NEST. Although the small number of events attributable to the exceptional prognosis of PTC resulted in decreased statistical power, we conducted power analyses to ensure that differences in survival were detectable. The current study used the most recently available patient survival status, and because Statistics Korea collects the survival status of all Koreans annually, future relinkage of the KCCR-NEST to Statistics Korea will enable greater patient follow-up. Another limitation of our study was being unable to adjust for RAI status. Our data set indicated that 53.5% of TT patients underwent RAI therapy, and 22.3% of LTT patients also received RAI therapy after the initial thyroidectomy. Although the high proportion of RAI therapy among LTT patients is somewhat contradictory, other studies showed high proportions of RAI administration in LTT patients as well (18.4%, 19.9%, and 33.2%, respectively).[10–12] As these studies also addressed,[10,11] a possible explanation may be that postsurgery

iodine scans for diagnostic purposes were coded inaccurately as RAI remnant ablation. Further sensitivity analysis adjusting for RAI status as given confirmed minimal changes in study results, and RAI status as given was not associated with patient survival in univariate or multivariate analyses.

In conclusion, we did not find a survival advantage of receiving a TT compared with LTT among Korean PTC patients overall or among different PTC risk groups, with the exception of a specific high-risk group (older females with larger tumors). The proportion of PTC patients who received a TT was 80% or greater regardless of risk group classification and 70% even in very low survival and recurrence risk patients. Accordingly, low-risk PTC patients in the current study may have received suboptimal treatment, for which the benefits of more aggressive treatment may not outweigh the harms of potential operative complications and the need for lifelong thyroid hormone replacement therapy. There does seem to be awareness of thyroid cancer overdiagnosis and unnecessarily aggressive treatment within the Korean population, and further individualized, patient-centered management may enhance the quality of life for those whose long-term prognosis is already excellent.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.surg.2018.08.030.

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