Current trends in the features of male thyroid cancer

Retrospective evaluation of their prognostic value

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Abstract

This study aimed to compare the clinicopathologic characteristics and oncologic outcomes of papillary thyroid cancer (PTC) patients according to sex. Then, we validated prognostic variables to determine whether sex is a significant prognostic factor for PTC.

Between January 2007 and December 2010, 1232 men and 7276 women PTC patients underwent surgery. The patient characteristics and 5-year oncologic outcomes were compared. The stepwise Cox proportional hazards model determined the significance of survival variables.

Men PTC patients had more lymph node (LN) metastases than women, both in the total ($P < .0001$) and hemithyroidectomy ($P < .0001$) patients. Men and women showed similar 5-year recurrence-free survivals, both in total ($P = .815$) and hemithyroidectomy ($P = .148$) patients. The tumor size and the number of positive central nodes were associated with tumor recurrence, but not sex.

Sex was not an independent prognostic factor for tumor recurrence. Multicenter clinical studies with long-term follow-ups are needed to validate these results.

Abbreviations: CCND = central compartment neck dissection, CI = confidence interval, CT = computed tomography, DSS = disease-specific survival, DTC = differentiated thyroid cancer, FNAB = fine needle aspiration biopsy, FTC = follicular thyroid cancer, thyroid cancer, HR = hazard radio, LN = lymph node, OS = overall survival, PMC = papillary microcarcinoma, pN1a = pathological N1a, PTC = papillary thyroid cancer, RAI = radioactive iodine, RFS = recurrence-free survival, Tg = thyroglobulin, TSH = thyroid-stimulating hormone, US = ultrasonography.

Keywords: male sex, oncologic outcome, papillary microcarcinoma, papillary thyroid cancer, sex disparity

1. Introduction

Sex is an important factor related to the pathogenesis, diagnosis, and prognosis of many diseases.[1] Sex disparities have been discovered in various cancers, and can easily be observed in sex-specific organs such as the breast, ovary, uterus, and prostate. However, differences in the incidence and/or prognosis are also shown in some sex-shared sites, including the thyroid, lung, and skin.[2,3]

The thyroid cancer incidence has increased worldwide over the last decade, making it one of the most common endocrine tumors.

It accounts for 1% of all cancers worldwide,[4] with a 6.6% annual percent change in the United States from 1997 to 2009.[5] The increased incidence is predominantly observed for tumors with papillary histology, with no significant changes seen in cases of follicular, medullary, or anaplastic histology. The increase includes mainly papillary microcarcinomas (PMCs), defined as tumors <1 cm, although the incidence of large tumors has also increased.[6,7]

With the rising incidence, thyroid cancer is currently the seventh most common malignancy in women; however, it is not among the most common 15 cancers in men. The 2002 GLOBOCAN database reported 103,589 female thyroid cancer cases worldwide, compared with 37,424 male cases, representing a female-to-male ratio of >2:1.[8] This sex disparity appears dominantly in differentiated thyroid cancer (DTC), such as papillary thyroid cancer (PTC) and follicular thyroid cancer (FTC), the incidence of which is 3-times higher in women than in men.[9]

Patients with thyroid cancer have a favorable prognosis, with the 10-year survival generally reported to exceed 90%. However, multiple studies have reported that men have a worse prognosis than women.[10–12] From the analysis of large retrospective uncontrolled studies, sex has been identified as a significant prognostic factor for thyroid cancer along with other parameters such as age, tumor size, histologic type, multicentricity, extrathyroidal extension, and lymph node (LN) metastases.[10,12] Among the several staging classifications for thyroid cancer, the Age, Metastases, Extent and Size and the European Organization

for the Research and Treatment of Cancer criteria include sex as a variable.[13,14]

Considering the sex differences in the incidence patterns, aggressiveness, and prognosis of thyroid cancer, the present study aimed to first identify and compare recent trends in clinicopathologic characteristics and oncologic outcomes of both male and female PTC patients. Second, we aimed to validate prognostic variables to determine whether sex is a significant prognostic indicator for PTC.

2. Methods

2.1. Patients

To discover recent trends of PTC, medical records of patients who were diagnosed with PTC from January 2007 to December 2010 were reviewed. A total of 8508 PTC patients, including 1232 male patients (14.5%) and 7276 female patients (85.5%), underwent thyroid surgery at the Department of Surgery in Yonsei University College of Medicine. Among them, hemi-thyroidectomy was performed for 250 male and 1501 female patients. Initially, comparative analyses were performed for all patients, followed by subgroup analyses among the hemi-thyroidectomy patients, according to sex. All procedures performed in this study were in accordance with the ethical standards of the Institutional Review Board of Yonsei University Health System (4–2016–0538) and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

2.2. Preoperative work-up

The preoperative patient work-up included physical examination, high-resolution staging ultrasonography (US), and neck computed tomography (CT). Thyroid nodules were diagnosed preoperatively based on US-guided fine needle aspiration biopsy (FNAB). In patients with DTC, the size and location of tumor, degree of extrathyroidal extension, nodal involvement, and other abnormal findings in the neck were complementarily evaluated by preoperative US and neck CT.[15] If a patient had clinically palpable LNs or a LN with a suspicious appearance on preoperative US, FNAB was performed for the LN. The presence of LN metastasis was determined by ultrasonography-guided FNAB or by the thyroglobulin (Tg) levels in the FNAB washout fluid (FNA-Tg >10 ng/mL, >the mean + 2SD of the FNA-Tg measured in node-negative patients, or >serum-Tg) from the LN.[16] Meanwhile, LN micrometastases were defined as metastatic deposits within a LN of <2 mm in diameter, which are rarely detected by US (clinical N0).[17]

2.3. Surgery

The criteria for the extent of surgery were determined in accordance with the American Thyroid Association guidelines.[18] Hemithyroidectomy was indicated if the following conditions were satisfied: patient age <45 years, a single lesion <1 cm in size, no definite extrathyroidal invasion, no LN metastasis on preoperative imaging studies, no personal history of the disease in the head or neck, and no first-degree family history of DTC. In all other cases, total thyroidectomy was indicated.

Prophylactic ipsilateral central compartment neck dissection (CCND) was conducted in all patients. The central compartment LNs consist of the level 6 LNs (pretracheal, prelaryngeal, and paraesophageal LNs), which include the LNs from the hyoid bone superior to the suprasternal notch inferiorly. On each side, the lateral boundary is limited by the medial border of the carotid sheath. For patients diagnosed with metastatic thyroid cancer in the lateral neck, neck dissection of levels IIa, III, IV, and VB was performed. The surgery followed the approaches of modified radical neck dissection type III for PTC, sparing the sternocleidomastoid muscle, spinal accessory nerve, and internal jugular vein. The LNs at levels IIB and VA were not routinely dissected.[19,20]

All patients were administered with levothyroxine for thyroid-stimulating hormone (TSH) suppression immediately postoperatively. Radioactive iodine (RAI) ablation was performed based on each patient's stage and risk factors, according to American Thyroid Association guidelines, at 4 to 12 weeks after surgery.[18] These patients underwent post-therapy whole-body scans and diagnostic whole-body scans 2 to 5 days after RAI ablation, and abnormal RAI uptakes were investigated.[21]

2.4. Outcome assessment

To evaluate oncologic outcomes, the TSH-suppressed serum Tg concentration was measured annually, and all patients underwent regular follow-up US. Patients with evidence of recurrence or distant metastasis were assessed using other imaging modalities, such as neck CT and/or positron emission tomography-CT. Regional neck node recurrence was confirmed by US-guided FNAB.

Overall survival (OS) was defined as the time from the date of initial surgery to the date of the last follow-up or death. Recurrence-free survival (RFS) was defined as the time from the surgery to the date of detection of the first recurrence on imaging.

2.5. Statistical analysis

Categorical data are reported as the rates and proportions, while the median and ranges were calculated for continuous data. Differences in continuous variables between men and women were compared using the Mann–Whitney U test or the Student t test, and differences in categorical variables were compared with the chi-square test or Fisher exact test, as appropriate. Patient characteristics and 5-year oncologic outcomes were compared in the 2 sex groups.

Survival curves were analyzed using the Kaplan–Meier method, and statistical significance was determined using the log-rank test. Significance of survival variables was analyzed by the stepwise Cox proportional hazards model. Univariate Cox regression analysis determined the correlation between each variable and RFS. Multivariate Cox regression analysis assessed whether sex was independently associated with RFS. P-values <.05 were considered statistically significant. All data were processed and statistically analyzed using IBM SPSS Statistics for Windows, version 23.0. (IBM Corp., Armonk, NY).

3. Results

3.1. Patient characteristics

Table 1 shows the clinicopathologic characteristics of the patients according to sex. Male patients underwent more total thyroidectomies with CCND and lateral neck dissection than women (16.4 vs 11.2%; $P < .001$). The median tumor size was larger (0.8 [0.5–1.2] vs 0.7 [0.5–1.1] cm; $P < .001$), and the median numbers of retrieved

Table 1

Clinicopathologic characteristics of study patients according to sex.

	Male	Female	P value
No. of patients	1232	7276	
Age, y	45 (38–55)	46 (37–54)	.404
Radiation history	5 (0.4)	24 (0.3)	.376
Family history	135 (10.1)	737 (10.1)	.375
Type of surgery			<.001
LTT+CCND	433 (35.1)	2780 (38.2)	
TT+CCND	598 (48.5)	3681 (50.6)	
TT+CCND+LND	201 (16.4)	815 (11.2)	
Hospital stay, d	3 (3–4)	3 (3–4)	.546
Tumor size, cm	0.8 (0.5–1.2)	0.7 (0.5–1.1)	<.001
Extrathyroidal extension, n (%)	634 (51.5)	3854 (53.0)	.325
Multiplicity, n (%)	25 (9.3)	156 (10.4)	.427
Bilaterality, n (%)	256 (20.8)	1518 (20.9)	.083
Total retrieved nodes	4 (2–9)	5 (2–9)	.374
Central nodes	4 (2–7)	5 (3–8)	.001
Lateral nodes	29 (20–46)	23 (8–33)	<.001
Total positive nodes	0 (0–3)	0 (0–1)	<.001
Central nodes	1 (0–2)	0 (0–1)	<.001
Lateral nodes	4 (1–8)	2 (0–5)	<.001
T classification, n (%)			.893
T1	568 (46.1)	3355 (46.1)	
T2	17 (1.4)	65 (0.9)	
T3	622 (50.5)	3714 (51.0)	
T4	25 (2.0)	142 (2.0)	
N classification, n (%)			<.001
N0	620 (50.3)	4737 (65.1)	
N1a	436 (35.4)	1933 (25.6)	
N1b	176 (14.3)	604 (8.3)	
M classification, n (%)			.227
M0	1227 (99.6)	7263 (99.8)	
M1	5 (0.4)	13 (0.2)	
TNM stage, n (%)			.167
I	798 (64.8)	4804 (66.0)	
II	7 (0.6)	13 (0.2)	
III	340 (27.6)	2122 (29.2)	
IV	87 (7.1)	337 (4.6)	
Pathology, n (%)			.035
PMC	753 (61.1)	4994 (68.6)	
Conventional PTC	408 (33.1)	1907 (26.2)	
Follicular variant	58 (4.7)	334 (4.6)	
Columnar variant	0 (0)	2 (0.02)	
Diffuse sclerosing variant	6 (0.5)	29 (0.4)	
Tall cell variant	0 (0)	1 (0.01)	
Insular variant	0 (0)	2 (0.02)	
Other	7 (0.6)	7 (0.1)	
Postoperative RAI ablation			
n (%)	715 (58.0)	3986 (54.8)	.032
Mean dose (mCi)	30 (0–30)	30 (0–30)	<.001

CCND = central compartment neck dissection, cm = centimeter, LND = lateral neck dissection, LTT = less than total thyroidectomy, mCi = millicurie, PMC = papillary microcarcinoma, PTC = papillary thyroid carcinoma, RAI = radioactive iodine, TNM = tumor-nodes-metastasis, TT = total thyroidectomy.

Table 2

Analysis of patients with tumor recurrence according to sex.

	Male	Female	P value
No. of patients	21	87	
Age, y	45.6 ± 18.6	44.7 ± 15.9	.456
Type of surgery, n (%)			.342
LTT+CCND	2	24	
TT+CCND	8	34	
TT+CCND+LND	11	29	
Tumor size, cm	1.5 ± 1.1	1.4 ± 1.0	.628
Extrathyroidal extension, n (%)	16 (76.2)	67 (77.0)	.937
Multiplicity, n (%)	3 (14.3)	15 (17.2)	.747
Bilaterality, n (%)	8 (38.1)	32 (36.8)	.912
Positive nodes	9.9 ± 10.3	6.7 ± 9.1	.193
Central nodes	5.2 ± 7.4	3.8 ± 3.8	.438
Lateral nodes	8.8 ± 4.9	7.6 ± 6.8	.588
T classification, n (%)			.965
T1	5 (23.8)	20 (23.0)	
T2	0 (0)	0 (0)	
T3	14 (66.7)	61 (70.1)	
T4	2 (9.5)	6 (6.9)	
N classification, n (%)			.067
N0	2 (9.5)	19 (21.8)	
N1a	8 (38.1)	40 (46.0)	
N1b	11 (52.4)	28 (32.2)	
M classification, n (%)			.842
M0	18 (85.7)	76 (87.4)	
M1	3 (14.3)	11 (12.6)	
TNM stage, n (%)			.721
I	11 (52.4)	43 (49.5)	
II	2 (9.5)	3 (3.4)	
III	3 (14.3)	21 (24.1)	
IV	5 (23.8)	20 (23.0)	
Postoperative RAI ablation			
n (%)	20 (95.2)	64 (73.6)	<.001
Mean dose	91.4 ± 66.7	52.0 ± 63.1	.012
Ablation success based on DxWBS, n (%)	18 (90.0)	50 (78.1)	.769
Recur-free duration, mo	62.8 ± 11.7	61.1 ± 15.9	.650
Recur site, L: D: L+D	16: 4: 0	70: 14: 1	.911
Treatment modality, OP: RAI	15: 5	64: 18	.897
Serum Tg after 5 years (without TSH↑), ng/mL	8.9 ± 29.2	38.8 ± 172.7	.456

CCND = central compartment neck dissection, cm = centimeter, D = distant, L = local, LND = lateral neck dissection, LTT = less than total thyroidectomy, OP = operation, RAI = radioactive iodine, Tg = thyroglobulin, TNM = tumor-nodes-metastasis, TSH = thyroid-stimulating hormone, TT = total thyroidectomy.

central (4 [2–7] vs 5 [3–8]; $P = .001$) and lateral neck nodes (29 [20–46] vs 23 [8–33]; $P < .001$) were higher in men. Furthermore, male patients had greater numbers of positive central (1 [0–2] vs 0 [0–1]; $P < .001$) and lateral neck nodes (4 [1–8] vs 2 [0–5]; $P < .001$), which resulted in significantly more frequent N1a and N1b stage tumors in male patients (49.7 vs 33.9%; $P < .001$). After surgery, larger number of male patients received RAI treatment (58.0 vs 54.8; $P = .032$). Higher median RAI dose was applied to male patients (30 [0–30] vs 30 [0–30] mCi; $P < .001$) (Table 1).

The median follow-up duration was 58 (range, 50–102) months. One hundred five male patients and 392 female patients were lost to follow-up.

3.2. Oncologic outcomes

The ablation success rates based on diagnostic whole-body scans were similar in the matched groups (95.7 vs 95.6%; $P = .746$). The TSH-suppressed serum Tg concentrations at 5 years after ablation were also similar (3.2 ± 13.6 vs 3.7 ± 24.9 ng/mL; $P = .593$). During the follow-up, 21 male and 87 female patients experienced tumor recurrence. The recurrence rates over 5 years were not significantly different between the 2 groups (1.7% vs 1.0%; $P = .531$). Patients with recurrence showed similar clinicopathologic features, recurrence-free period, site of recurrence, treatment modality, and serum Tg concentration at 5 years (Table 2). There was no disease-specific mortality during the follow-up period.
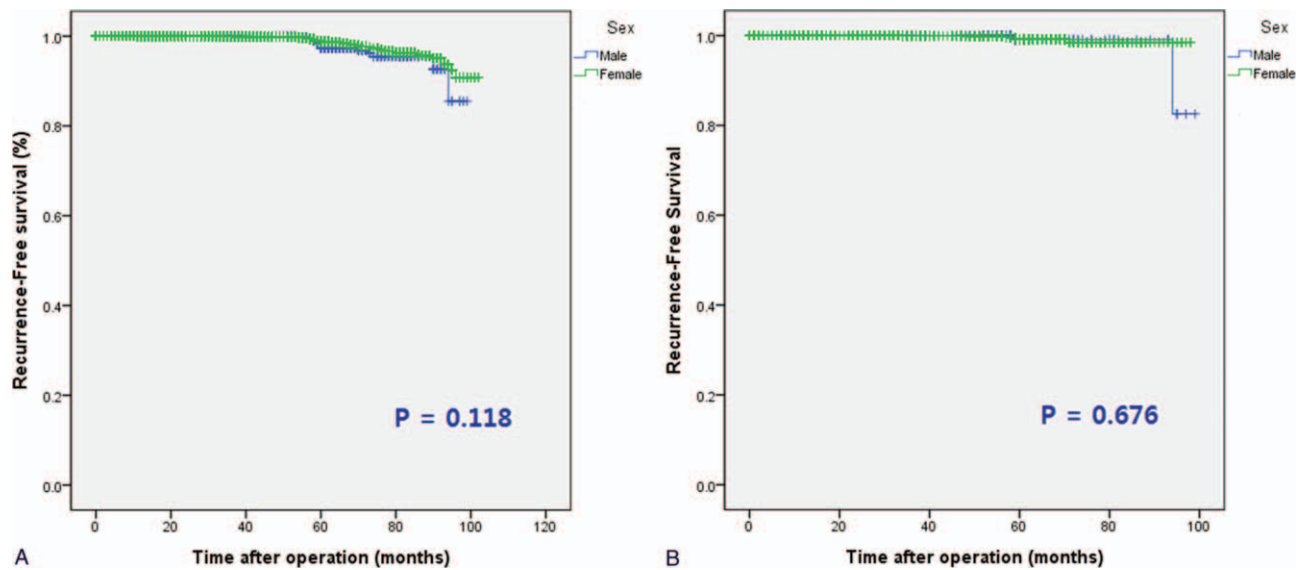
Figure 1. Kaplan–Meier estimates of recurrence-free survival in (A) all patients and (B) hemithyroidectomy patients according to sex.

The 5-year median RFS did not differ significantly between the 2 groups (55.7±17.8 vs 59.0±17.9 months; P=.118) (Fig. 1A).

3.3. Recurrence-free survival (RFS) analysis

Univariate survival analyses were performed to determine the correlations between sex and other clinicopathological characteristics and RFS. No difference in RFS was found between male and female patients (hazard ratio [HR] 1.529, 95% confidence interval [CI] 0.949–2.463). Subsequently, multiple Cox survival analyses were performed for RFS to show that mean tumor size

was associated with RFS. Sex was not an independent predictor of RFS (Table 3).

3.4. Subanalyses of patients treated with hemithyroidectomy

Further assessment of the PTC patients who underwent hemithyroidectomy from January 2007 to December 2010 was conducted. As a result, male patients were found to be older (44 [37–52] vs 42 [35–50] years; P=.007). The median number of retrieved central neck nodes was higher in female patients (3 [2–

Table 3

Stepwise Cox regression analysis of PTC patients.

	Univariate analysis			Multivariate analysis		
	Hazard ratio	95% CI	P value	Hazard ratio	95% CI	P value
Sex (male vs female)	1.529	(0.949–2.463)	.081	1.517	(0.616–3.736)	.365
Age, y	0.988	(0.972–1.004)	.150			
Family history	0.727	(0.421–1.255)	.252			
Type of surgery						
TT vs LTT	0.271	(0.164–0.446)	<.001	NA		
TT+LND vs LTT	0.286	(0.185–0.442)	<.001	NA		
Tumor size, cm	1.721	(1.503–1.970)	<.001	1.306	(1.003–1.701)	.047
Extrathyroidal extension	0.352	(0.225–0.550)	<.001	0.310	(0.092–1.049)	.060
Multiplicity	1.547	(0.932–2.566)	.091			
Bilaterality	0.495	(0.335–0.732)	.001	0.754	(0.369–1.541)	.439
Positive nodes						
Central nodes	1.185	(1.151–1.220)	<.001	1.063	(0.996–1.134)	.067
Lateral nodes	1.085	(1.050–1.120)	<.001	1.026	(0.974–1.080)	.339
TNM stage						
2 vs 1	0.180	(0.112–0.239)	<.001	0.546	(0.258–1.155)	.113
3 vs 1	3.139	(1.198–8.222)	.020	NA		
4 vs 1	0.171	(0.097–0.299)	<.001	0.401	(0.084–1.913)	.252
PTC subtype						
PMC vs conventional	1.195	(0.542–2.636)	.658			
Others vs conventional	0.456	(0.206–1.010)	.053			
RAI abrasion treatment	1.011	(1.007–1.014)	.011	0.998	(0.992–1.004)	.585

cm = centimeter, LND = lateral neck dissection, LTT = less than total thyroidectomy, PMC = papillary microcarcinoma, PTC = papillary thyroid carcinoma, RAI = radioactive iodine, TNM = tumor-nodes-metastasis, TT = total thyroidectomy.

Table 4

Clinicopathologic characteristics of hemithyroidectomy patients according to sex.

	Male	Female	P value
No. of patients	269	1509	
Age, y	44 (37–52)	42 (35–50)	.007
Radiation history	0 (0)	3 (0.2)	.465
Family history	26 (9.6)	143 (9.5)	.950
Hospital stay, d	3 (3–3)	3 (3–3)	.113
Tumor size, cm	0.5 (0.4–0.7)	0.5 (0.3–0.7)	.008
Extrathyroidal extension, n (%)	77 (28.5)	460 (30.6)	.432
Multiplicity, n (%)	25 (9.3)	156 (10.4)	.580
Retrieved central nodes	3 (2–6)	4 (2–7)	.002
Positive central nodes	0 (0–1)	0 (0–0)	<.001
T classification, n (%)			.384
T1	192 (71.4)	1032 (68.4)	
T2	0 (0)	10 (0.7)	
T3	77 (28.6)	466 (30.9)	
T4	0 (0)	1 (0)	
N classification, n (%)			<.001
N0	187 (69.5)	1222 (81.0)	
N1a	82 (30.5)	287 (19.0)	
TNM stage, n (%)			.161
I	212 (78.8)	1245 (82.5)	
II	0 (0)	2 (0.1)	
III	57 (21.2)	262 (17.4)	
IV	0 (0)	0 (0)	
Pathology, n (%)			.600
PMC	243 (90.3)	1378 (91.3)	
Conventional PTC	10 (3.7)	56 (3.7)	
Follicular variant	16 (6.0)	75 (5.0)	

cm = centimeter, PMC = papillary microcarcinoma, PTC = papillary thyroid carcinoma, TNM = tumor-nodes-metastasis.

Table 5

Analysis of hemithyroidectomy patients with tumor recurrence according to sex.

	Male	Female	P value
No. of patients	2	8	
Age, y	39.0 ± 0.0	38.6 ± 11.7	.967
Tumor size, cm	1.0 ± 0.0	0.5 ± 0.5	.242
Extrathyroidal extension, n (%)	1 (50.0)	6 (75.0)	.545
Multiplicity, n (%)	1 (50.0)	1 (12.5)	.189
Positive central nodes	3.0 ± 2.8	1.0 ± 1.8	.252
T classification, n (%)			.545
T1	1 (50.0)	2 (25.0)	
T2	0 (0)	0 (0)	
T3	1 (50.0)	6 (71.0)	
T4	0 (0)	0 (0)	
N classification, n (%)			.011
N0	0 (0)	5 (65.1)	
N1a	2 (100)	3 (25.6)	
M classification, n (%)			.842
M0	18 (85.7)	76 (87.4)	
M1	3 (14.3)	11 (12.6)	
TNM stage, n (%)			.486
I	2 (100)	6 (66.0)	
II	0 (0)	0 (0)	
III	0 (0)	2 (29.2)	
IV	0 (0)	0 (0)	
Recur-free duration, mo	76.5 ± 24.7	55.0 ± 10.7	.075
Recur site, L: D: L+D	2: 0: 0	8: 0: 0	>.999
Treatment modality, OP: RAI	2: 0	8: 0	>.999
Serum Tg after 5 years (without TSH↑), ng/mL	0.5 ± 0.7	2.8 ± 6.7	.643

cm = centimeter, D = distant, L = local, OP = operation, RAI = radioactive iodine, Tg = thyroglobulin, TNM = tumor-nodes-metastasis, TSH = thyroid-stimulating hormone.

6] vs 4 [2–7]; $P = .002$), whereas male patients had a greater number of positive central neck nodes (0 [0–1] vs 0 [0–0]; $P < .001$), and consequently more frequent N1a stage tumors (30.4 vs 19.0%; $P < .001$) (Table 4).

Recurrence was detected in 2 male and 8 female patients after 5 years. The recurrence rates were similar in the 2 groups (0.7 vs 0.5%; $P = .672$). Patients with recurrence had similar clinicopathologic features, postoperative RAI treatment, recurrence-free period, site of recurrence, treatment modality, and serum Tg concentration after 5 years (Table 5).

The 5-year median RFS showed no significant difference between the 2 groups ($54.2 ± 18.5$ vs $66.0 ± 16.9$ months; $P = .676$) (Fig. 1B).

Univariate and multiple Cox regression analyses were repeated for hemithyroidectomy patients. Univariate analysis revealed no difference in RFS between male and female patients (HR 1.327, 95% CI 0.278–6.323). Multivariate Cox survival analyses showed that the number of positive central neck nodes was an independent predictor of RFS, whereas sex was not an independent predictor of RFS (Table 6).

Table 6

Stepwise Cox regression analysis of hemithyroidectomy patients.

	Univariate analysis			Multivariate analysis		
	Hazard ratio	95% CI	P value	Hazard ratio	95% CI	P value
Sex (male vs female)	1.267	(0.262–6.037)	.775	1.305	(0.295–6.567)	.747
Age, y	0.955	(0.897–1.017)	.154			
Family history	0.266	(0.068–1.036)	.056			
Tumor size, cm	1.575	(0.593–4.184)	.326			
Extrathyroidal extension	0.184	(0.048–0.711)	.014	0.246	(0.059–1.014)	.052
Multiplicity	0.585	(0.119–2.869)	.509			
Positive nodes						
Central nodes	1.405	(1.095–1.802)	.007	1.314	(1.007–1.714)	.044
TNM stage						
Others vs1	0.808	(0.171–3.805)	.787			
PTC subtype						
Others vs conventional	1.229	(0.154–9.384)	.846			

cm = centimeter, PTC = papillary thyroid carcinoma, TNM = tumor-nodes-metastasis.

To investigate the appropriate cutoff tumor size that yields similar nodal status in hemithyroidectomy patients, the chi-square test was performed for sex and N stage in all final pathologic tumor sizes. A tumor size ≤ 0.25 cm was significantly associated with the similar nodal status between the 2 sex groups.

Moreover, we compared pathological N1a (pN1a) patients who received hemithyroidectomy. Eighty-two male and 161 female patients were analyzed and showed similar rates of LN micrometastases according to preoperative staging US (79.3 vs 81.7%; $P = .962$). US also revealed similar sizes of suspicious LNs in the 2 groups (0.5 ± 0.2 vs 0.6 ± 0.2 cm; $P = .203$).

4. Discussion

Thyroid cancer is one of the most common endocrine malignancies; it shows notable sex disparities, with a higher incidence in women and worse prognosis in men.[8,10–12,22] The sex difference in incidence is remarkable in DTCs, such as PTC and FTC, for which the incidence is 3 times higher in women than in men.

PTC is the most common histologic type, accounting for approximately 80% of cases. Its incidence has nearly doubled in the last few decades, contributing to the remarkable increase in the overall thyroid cancer incidence worldwide.[9] While this may be due to the earlier diagnosis of subclinical disease,[23] little is currently known about the factors responsible for the dramatic increase in PTC.

Investigations regarding the causes of these sex disparities have been conducted previously. Radiation exposure[24] and dietary iodine,[25] well-known environmental risk factors for thyroid cancer, do not appear to account for these disparities. Clinical and epidemiologic studies have provided no consistent evidence regarding common somatic genetic alterations such as BRAF V600E, that are rearranged in transformation/papillary thyroid carcinomas, or neurotrophin receptor tyrosine kinase 1 mutations contributing to the thyroid cancer sex differences.[26,27] Recent studies have suggested that the estrogen and estrogen hormone receptor status in thyroid cancer cells may promote cell proliferation in thyroid cancer; however, there is no conclusive evidence to confirm the correlation between sex hormones and these disparities.[28,29]

Male sex was associated with a higher mortality and lower disease-free survival in most previous studies, and men show worse OS and disease-specific survival (DSS) with more recurrence.[30–39] Meanwhile, other studies have shown no sex differences, presenting with the unaffected OS and DSS.[30,36,40–42] Thus, a male survival disadvantage is not a consistent finding, and the impact of sex on recurrences of DTC is not yet substantiated.

Herein, we analyzed and compared the clinicopathologic characteristics and oncologic outcomes of male and female PTC patients. The study period included PTC patients from 2007 to 2010 for 2 reasons: to involve cases representative of the recent trends in PTC, and to assess the 5-year oncologic outcomes. Moreover, the stepwise Cox proportional hazards model was created to evaluate significant survival variables. First, univariate Cox regression analysis identified the correlations between each variable and RFS. Second, multivariate Cox regression analysis was performed to discover whether sex was independently associated with RFS.

Our analyses revealed that male PTC patients had significantly more LN metastases than females, both in the central and lateral neck areas. However, despite the different nodal statuses, the 2 groups showed similar 5-year median RFS. Sex was not an independent prognostic factor for tumor recurrence. According to our data, tumor size was associated with prognosis of PTC, and the number of positive central nodes had prognostic capacity in hemithyroidectomy patients.

Tumor size was traditionally considered a prognostic factor for disease recurrence, and the extent of surgery as well as RAI treatment after surgery is largely determined by tumor size. PTCs were generally divided into PMC and conventional PTC on the basis of a tumor diameter of 1.0 cm. However, the previous studies have reported controversial recurrence rates according to tumor size cutoff of 1.0 cm. Recent studies provide the optimal tumor size cutoff of 1.8 to 2.0 cm for predicting the risk of recurrence.[43,44] Moreover, many international groups have also revealed the prognostic significance of increasing number and ratio of positive LNs in DTC.[45–47] These findings are comparable to our study.

Although the reason for the similar RFS between male and female PTC patients shown in this study remains difficult to explain, it may be partially due to the long-term trend of decreasing prognostic potential of male sex. One study has reported secular trends in the prognostic factors for PTC. The risk for tumor recurrence associated with male sex decreased over time, while the risk associated with pathologic characteristics either remained the same or increased. Such results suggest that the reasons behind this trend may be the change in clinical characteristic of PTC and increased early detection of cancer in male patients.[48]

In hemithyroidectomy patients, those with a tumor size of ≤ 0.25 cm were found to have similar N stages. Small-sized PMCs rarely metastasize to the LNs, both in men and women. Thus, early-stage thyroid cancers such as tiny PMC may not show considerable sex difference in LN involvement. We furthermore found that the 82 male and 161 female pN1a hemithyroidectomy patients had similar rates of LN micrometastases and similar sizes of suspicious LNs. Male PTC patients may have more metastatic potential to the LNs than females; however, the metastatic LNs themselves may show similar cancer behaviors and traits, especially in early-stage thyroid cancers.

This study has several limitations. First, the analysis was based on a limited group of patients. Even with the existing indications of total thyroidectomy and hemithyroidectomy, the early days of thyroid surgery tend to be rather aggressive. In the early- and mid-2000s, total thyroidectomy was predominantly performed in thyroid cancer patients. Hence, our comparative analyses involved patients treated from 2007, during which the number of less than total thyroidectomies gradually increased. Second, the study population was from a single center. Our institution offers a well-developed screening program for thyroid cancer patients, and a substantial amount of early-stage PTCs may have been included. Moreover, we routinely perform prophylactic ipsilateral CCND to all thyroid cancer patients. Results of this study should be interpreted while considering these backgrounds. Third, as PTC has a relatively favorable prognosis and mild biological behavior, long-term follow-up data on the oncologic outcomes are needed to validate our results.

Despite the aforementioned limitations, the present study is the first to compare the oncologic outcomes of PTC patients according to sex. We believe that our study has provided some novel viewpoints on current trends in male PTC patient prognosis. The overall increasing incidence of PMC that suggests

prompt diagnosis and treatment in the recent era should alert clinicians to carefully consider the disease characteristics themselves, not just sex differences. This study suggests that aggressive pathologic factors have more impact on disease prognosis than sex. The prognostic indicators for PTC, including large tumor size or LN metastases, should be focused on to provide proper treatment. Based on past statistical data, male sex linked to more aggressive treatment can possibly be a fallacy of generalization. Our results provide a good starting point to guide future studies.

5. Conclusion

Despite the higher metastatic potential for the LNs in male PTC patients, sex was not an independent prognostic factor for tumor recurrence. The similar oncologic outcomes and the similar traits of metastatic LNs among men and women indicate that excessive treatments in male PTC patients compared with females may not be warranted, especially in cases of PMC. Multicenter clinical studies with long-term follow-ups are needed to validate these results.

Author contributions

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References

[1] Institute of Medicine. (US) Committee on understanding the biology of sex and gender differences. In: Wizemann TM, Pardue ML, editors. Exploring the Biological Contributions to Human Health: Does Sex Matter? Washington (DC): National Academies Press (US); 2001. Available at: https://www.ncbi.nlm.nih.gov/books/NBK222288/ doi:10.17226/10028. Accessed December 21, 2016.

[2] Cook MB, Dawsey SM, Freedman ND, et al. Sex disparities in cancer incidence by period and age. Cancer Epidemiol Biomarkers Prev 2009;18:1174–82.

[3] Cook MB, McGlynn KA, Devesa SS, et al. Sex disparities in cancer mortality and survival. Cancer Epidemiol Biomarkers Prev 2011;20:1629–37.

[4] Parkin DM, Bray F, Ferlay J, et al. Global cancer statistics, 2002. CA Cancer J Clin 2005;55:74–108.

[5] Cancer of The Thyroid-SEER Stat Fact Sheets. Accessed December 21, 2016.

[6] Enewold L, Zhu K, Ron E, et al. Rising thyroid cancer incidence in the United States by demographic and tumor characteristics, 1980-2005. Cancer Epidemiol Biomarkers Prev 2009;18:784–91.

[7] Kent WD, Hall SF, Isotalo PA, et al. Increased incidence of differentiated thyroid carcinoma and detection of subclinical disease. Cmaj 2007;177:1357–61.

[8] Ferlay J, Soerjomataram I, Dikshit R, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer 2015;136:E359–86.

[9] Aschebrook-Kilfoy B, Ward MH, Sabra MM, et al. Thyroid cancer incidence patterns in the United States by histologic type, 1992-2006. Thyroid 2011;21:125–34.

[10] Johnston LE, Tran Cao HS, Chang DC, et al. Sociodemographic predictors of survival in differentiated thyroid cancer: results from the SEER Database. ISRN Endocrinol 2012;2012:384707.

[11] Schlumberger MJ. Papillary and follicular thyroid carcinoma. N Engl J Med 1998;338:297–306.

[12] Gilliland FD, Hunt WC, Morris DM, et al. Prognostic factors for thyroid carcinoma. A population-based study of 15,698 cases from the Surveillance, Epidemiology and End Results (SEER) program 1973-1991. Cancer 1997;79:564–73.

[13] Brierley JD, Panzarella T, Tsang RW, et al. A comparison of different staging systems predictability of patient outcome. Thyroid carcinoma as an example. Cancer 1997;79:2414–23.

[14] Dean DS, Hay ID. Prognostic indicators in differentiated thyroid carcinoma. Cancer Control 2000;7:229–39.

[15] Hoang JK, Branstetter BF4th, Gafton AR, et al. Imaging of thyroid carcinoma with CT and MRI: approaches to common scenarios. Cancer Imaging 2013;13:128–39.

[16] Kim MJ, Kim EK, Kim BM, et al. Thyroglobulin measurement in fine-needle aspirate washouts: the criteria for neck node dissection for patients with thyroid cancer. Clin Endocrinol (Oxf) 2009;70:145–51.

[17] Siegel RJ. Surgical pathology of lymph nodes in cancer staging: routine and specialized techniques. Surg Oncol Clin N Am 1996;5:25–31.

[18] Cooper DS, Doherty GM, Haugen BR, et al. Revised American Thyroid Association management guidelines for patients with thyroid nodules and differentiated thyroid cancer. Thyroid 2009;19:1167–214.

[19] Caron NR, Clark OH. Papillary thyroid cancer: surgical management of lymph node metastases. Curr Treat Options Oncol 2005;6:311–22.

[20] Caron NR, Tan YY, Ogilvie JB, et al. Selective modified radical neck dissection for papillary thyroid cancer-is level I, II and V dissection always necessary? World J Surg 2006;30:833–40.

[21] Lee S, Lee CR, Lee SC, et al. Surgical completeness of robotic thyroidectomy: a prospective comparison with conventional open thyroidectomy in papillary thyroid carcinoma patients. Surg Endosc 2014;28:1068–75.

[22] Rahbari R, Zhang L, Kebebew E. Thyroid cancer gender disparity. Future Oncol 2010;6:1771–9.

[23] Chen AY, Jemal A, Ward EM. Increasing incidence of differentiated thyroid cancer in the United States, 1988-2005. Cancer 2009;115:3801–7.

[24] Ron E, Lubin JH, Shore RE, et al. Thyroid cancer after exposure to external radiation: a pooled analysis of seven studies. Radiat Res 1995;141:259–77.

[25] Horn-Ross PL, Morris JS, Lee M, et al. Iodine and thyroid cancer risk among women in a multiethnic population: the Bay Area Thyroid Cancer Study. Cancer Epidemiol Biomarkers Prev 2001;10:979–85.

[26] Lee JH, Lee ES, Kim YS. Clinicopathologic significance of BRAF V600E mutation in papillary carcinomas of the thyroid: a meta-analysis. Cancer 2007;110:38–46.

[27] Brzezianska E, Karbownik M, Migdalska-Sek M, et al. Molecular analysis of the RET and NTRK1 gene rearrangements in papillary thyroid carcinoma in the Polish population. Mutat Res 2006;599:26–35.

[28] Zeng Q, Chen G, Vlantis A, et al. The contributions of oestrogen receptor isoforms to the development of papillary and anaplastic thyroid carcinomas. J Pathol 2008;214:425–33.

[29] Rajoria S, Suriano R, Shanmugam A, et al. Metastatic phenotype is regulated by estrogen in thyroid cells. Thyroid 2010;20:33–41.

[30] Akslen LA, Haldorsen T, Thoresen SO, et al. Survival and causes of death in thyroid cancer: a population-based study of 2479 cases from Norway. Cancer Res 1991;51:1234–41.

[31] Akslen LA, Myking AO, Salvesen H, et al. Prognostic importance of various clinicopathological features in papillary thyroid carcinoma. Eur J Cancer 1992;29A:44–51.

[32] Carcangiu ML, Zampi G, Pupi A, et al. Papillary carcinoma of the thyroid. A clinicopathologic study of 241 cases treated at the University of Florence, Italy. Cancer 1985;55:805–28.

[33] Cunningham MP, Duda RB, Recant W, et al. Survival discriminants for differentiated thyroid cancer. Am J Surg 1990;160:344–7.

[34] Mazzaferri EL, Jhiang SM. Long-term impact of initial surgical and medical therapy on papillary and follicular thyroid cancer. Am J Med 1994;97:418–28.

[35] Mazzaferri EL, Kloos RT. Clinical review 128: current approaches to primary therapy for papillary and follicular thyroid cancer. J Clin Endocrinol Metab 2001;86:1447–63.

[36] Micheli A, Ciampichini R, Oberaigner W, et al. The advantage of women in cancer survival: an analysis of EUROCARE-4 data. Eur J Cancer 2009;45:1017–27.

[37] Samaan NA, Schultz PN, Hickey RC, et al. The results of various modalities of treatment of well differentiated thyroid carcinomas: a retrospective review of 1599 patients. J Clin Endocrinol Metab 1992;75:714–20.

[38] Toniato A, Boschin I, Casara D, et al. Papillary thyroid carcinoma: factors influencing recurrence and survival. Ann Surg Oncol 2008;15:1518–22.

[39] Tubiana M, Schlumberger M, Rougier P, et al. Long-term results and prognostic factors in patients with differentiated thyroid carcinoma. Cancer 1985;55:794–804.

[40] Elisei R, Molinaro E, Agate L, et al. Are the clinical and pathological features of differentiated thyroid carcinoma really changed over the last 35 years? Study on 4187 patients from a single Italian institution to answer this question. J Clin Endocrinol Metab 2010;95:1516–27.

[41] Mihailovic J, Stefanovic L, Malesevic M. Differentiated thyroid carcinoma with distant metastases: probability of survival and its predicting factors. Cancer Biother Radiopharm 2007;22:250–5.

[42] Shah JP, Loree TR, Dharker D, et al. Prognostic factors in differentiated carcinoma of the thyroid gland. Am J Surg 1992;164:658–61.

[43] Hwangbo Y, Kim JM, Park YJ, et al. Long-term recurrence of small papillary thyroid cancer and its risk factors in a Korean multicenter study. J Clin Endocrinol Metab 2017;102:625–33.

[44] Machens A, Holzhausen HJ, Dralle H. The prognostic value of primary tumor size in papillary and follicular thyroid carcinoma. Cancer 2005;103:2269–73.

[45] Ito Y, Jikuzono T, Higashiyama T, et al. Clinical significance of lymph node metastasis of thyroid papillary carcinoma located in one lobe. World J Surg 2006;30:1821–8.

[46] Lee J, Song Y, Soh EY. Prognostic significance of the number of metastatic lymph nodes to stratify the risk of recurrence. World J Surg 2014;38:858–62.

[47] Leboulleux S, Rubino C, Baudin E, et al. Prognostic factors for persistent or recurrent disease of papillary thyroid carcinoma with neck lymph node metastases and/or tumor extension beyond the thyroid capsule at initial diagnosis. J Clin Endocrinol Metab 2005;90:5723–9.

[48] Choi H, Lim JA, Ahn HY, et al. Secular trends in the prognostic factors for papillary thyroid cancer. Eur J Endocrinol 2014;171:667–75.