Male Patients With Papillary Thyroid Cancer Have a Higher Risk of Extranodal Extension

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Abstract

Purpose: There is a sex disparity in papillary thyroid cancer (PTC). Male sex is associated with a higher likelihood of advanced stage disease. This study aimed to examine the significance of sex for extranodal extension (ENE) in PTC.

Patients and Methods: We reviewed the data of PTC patients who had undergone initial surgical resection from July 2012 to December 2014 (N = 1531). The effects of sex and other clinicopathological factors on ENE were investigated.

Results: Of 1531 patients identified, 377 (24.6%) were male, 816 (53.3%) had positive nodes, and 256 (16.7%) had ENE. Compared with female patients, male patients had a higher risk of ENE ($P < 0.001$). Multivariable analysis of clinicopathological factors revealed that male sex (odds ratio [OR], 1.98; 95% confidence interval [CI], 1.37 - 2.87; $P < 0.001$), age older than 60 years (OR, 1.93; 95% CI, 1.08 - 3.35; $P = 0.023$), extrathyroidal extension (OR, 3.52; 95% CI, 2.42 - 5.14; $P < 0.001$), bilateral multifocality (OR, 2.18; 95% CI, 1.53 - 3.13; $P < 0.001$), and more positive nodes were significantly associated with increased risk of ENE. Patients with 6-10 positive nodes were 16.45-fold higher to have ENE than patients with 5 positive nodes or less (95% CI, 11.07 - 24.68; $P < 0.001$).

Conclusion: Male PTC patients had a higher risk of ENE than female. Sex was an independent predictor of ENE. The underlying mechanism needs to be investigated further.

Introduction

Patients with papillary thyroid cancer (PTC) are prone to have metastatic nodes in central and lateral neck[1]. Some metastatic nodes may present with more aggressive characteristics, such as extranodal extension (ENE)[2]. The clinical role of ENE remains to be investigated. Some studies have found that ENE is associated with higher risks of recurrence[2, 3], poor survival[4], and nonexcellent response to initial therapy[5].

Sex plays an important role in PTC patients[6]. Male patients are associated with advanced stage disease and aggressive histopathology[7, 8]. Male PTC patients have worse outcomes than female diagnosed at age younger than 55 years[6, 8]. Men have a shorter disease specific survival and have higher thyroid cancer-specific mortality[7]. However, there is still a debate as to whether or not sex is an independent risk factor for survival in PTC [9, 10, 7, 8, 11].

In this study, we aimed to examine the association between sex and ENE in PTC patients at a single institution.

Patients And Methods

Patient Cohort

This retrospective study was approved by the Institutional Review Board of the Affiliated Cancer Hospital of Zhengzhou University. Medical records of consecutive PTC patients who had undergone surgical resection at our center between July 2012 and December 2014 were reviewed. The inclusion criteria were a diagnosis of PTC, undergoing initial surgery, and surgical procedures including at least hemithyroidectomy and ipsilateral central neck dissection. The exclusion criteria were a diagnosis of non-PTC, undergoing reoperation, or surgical procedures without neck dissection. Analyses for ENE were performed on all eligible patients.

ENE was defined as the extension of metastatic cells beyond the nodal capsule into the perinodal soft tissue[12]. ENE could be detected intraoperatively with the naked eyes or be identified based on the final pathology reports. Tumor size was defined as the maximum diameter measured by preoperative ultrasound. ETE and bilateral multifocality were confirmed on the final pathological reports. Patients were classified according to the eighth edition of AJCC/TNM staging system for thyroid cancer.

Statistical Analysis

Fisher's exact test was used to assess categorical variables, and analysis of variance was used to assess continuous variables. To quantify the impact of baseline clinicopathological factors on the likelihood of ENE, logistic regression models with single variable of interest were fit to identify significant predictors. In models containing continuous variables, restricted cubic splines were used to test for possible nonlinearity of the effects. When significant ($P < 0.05$) nonlinearity as a function of a variable was found, the effect curve was plotted with 95% confidence bands for visual inspection[13, 14]. And this variable was transformed into a categorical variable for further analysis. Statistically and clinically significant variables were carried forward to multivariate logistic regression models. Statistical analyses were conducted using R language (<http://www.r-project.org/>). All statistical tests were two tailed, and results were considered significant at $p < 0.05$.

Results

Of the 1531 PTC patients included in this study cohort, 24.6% were men, 19.1% had ETE, 26.1% had bilateral disease, 53.3% had metastatic lymph nodes, and 16.7% had ENE. Mean age at the time of resection was 44.81 ± 11.57 years (range, 10 to 80 years), and mean tumor size was 14.77 ± 10.73 mm. Baseline patient demographics and disease characteristics are listed in Table 1.

Table 1
Demographic and Tumor Characteristics of 1531 PTC Patients Stratified by Gender

Characteristic	All patients	Female	Male	<i>p</i> value
	No. (%)	No. (%)	No. (%)	
Total No. of patients	1531 (100)	1154 (75.4)	377 (24.6)	
Age (years)				0.086†
Mean ± SD	44.81 ± 11.57	45.1 ± 11.53	43.92 ± 11.65	
Tumor size (mm)				0.211†
Mean ± SD	14.77 ± 10.73	14.57 ± 10.43	15.37 ± 11.57	
Management of primary tumor				0.030*
Hemithyroidectomy	343 (22.4)	242 (21.0)	101 (26.8)	
Total thyroidectomy	1008 (65.8)	767 (66.5)	241 (63.9)	
Hemithyroidectomy with partial resection of the opposite lobe	180 (11.8)	145 (12.5)	35 (9.3)	
CND				0.433*
Ipsilateral	1088 (71.1)	814 (70.5)	274 (72.7)	
Bilateral	443 (28.9)	340 (29.5)	103 (27.3)	
LND				0.019*
No	307 (20.1)	250 (21.7)	57 (15.1)	
Ipsilateral	910 (59.4)	673 (58.3)	237 (62.9)	
Bilateral	314 (20.5)	231 (20.0)	83 (22.0)	
ETE				0.497*
No	1239 (80.9)	929 (80.5)	310 (82.2)	
Yes	292 (19.1)	225 (19.5)	67 (17.8)	
Bilateral multifocality				0.544*
No	1131 (73.9)	857 (74.3)	274 (72.7)	

Characteristic	All patients	Female	Male	<i>p</i> value
	No. (%)	No. (%)	No. (%)	
Yes	400 (26.1)	297 (25.7)	103 (27.3)	
Pathological T classification				0.559*
T1	1036 (67.7)	775 (67.2)	262 (69.5)	
T2	186 (12.1)	148 (12.8)	38 (10.1)	
T3	153 (10.0)	113 (9.8)	39 (10.3)	
T4	156 (10.2)	118 (10.2)	38 (10.1)	
Pathological N classification				< 0.001*
N0	715 (46.7)	582 (50.4)	133 (35.3)	
N1a	307 (20.1)	219 (19.0)	88 (23.3)	
N1b	509 (33.2)	353 (30.6)	156 (41.4)	
No. of positive nodes				< 0.001†
Mean ± SD	2.61 ± 4.21	2.40 ± 4.07	3.27 ± 4.53	
Lymph node yield				0.068†
Mean ± SD	13.5 ± 11.76	13.19 ± 11.49	14.47 ± 12.53	
ENE				< 0.001*
No	1275 (83.3)	987 (85.5)	288 (76.4)	
Yes	256 (16.7)	167 (14.5)	89 (23.6)	
Abbreviations: PTC, papillary thyroid carcinoma; CND, central neck dissection; LND, lateral neck dissection; ENE, extranodal extension; ETE, extrathyroidal extension; SD, standard deviation.				
*Fisher's exact test was used. †Analysis of variance (ANOVA) was used.				

More men were diagnosed with pathological N1 disease ($P < 0.001$). Men had more positive nodes and a higher risk of ENE than women ($P < 0.001$). Men also had a higher risk of lateral neck dissection ($P = 0.019$). There was no difference in age, tumor size, ETE, and bilateral multifocality between men and women (Table 1).

In univariate analyses, factors significantly associated with ENE were men versus women (OR, 1.83; 95% CI, 1.36 to 2.43; $P < 0.001$), ETE versus no ETE (OR, 3.96; 95% CI, 2.95 to 5.30; $P < 0.001$), bilateral disease versus unilateral disease (OR, 3.20; 95% CI, 2.42 to 4.23; $P < 0.001$), tumor size 21–40 mm versus tumor size 20 mm or less (OR, 3.25; 95% CI 2.39 to 4.43; $P < 0.001$), and having 6–10 positive nodes versus having 5 positive nodes or less (OR, 16.16; 95% CI, 11.17 to 23.39; $P < 0.001$). Age was marginally associated with ENE (Table 2).

Table 2
Univariate Association Between ENE and Clinicopathological Characteristics in 1531 PTC Patients

Characteristic	Without ENE (N = 1275)	With ENE (N = 256)	Odds ratio	95% CI	p value
	No. (%)	No. (%)			
Gender					
Female	987 (77.4)	167 (65.2)	1.00		
Male	288 (22.6)	89 (34.8)	1.83	1.36–2.43	< 0.001
Age (years)					
31–60	1028 (80.6)	188 (73.4)	1.00		
≤ 30	149 (11.7)	40 (15.6)	1.47	1.00–2.15	0.049
≥ 61	98 (7.7)	28 (11.0)	1.56	0.99–2.44	0.051
Tumor size (mm)					
≤ 20	1068 (83.8)	155 (60.6)	1.00		
21–40	180 (14.1)	85 (33.2)	3.25	2.39–4.43	< 0.001
≥ 41	27 (2.1)	16 (6.2)	4.08	2.15–7.75	< 0.001
No. of positive nodes					
≤ 5	1174 (92.1)	92 (35.9)	1.00		
6–10	75 (5.9)	95 (37.1)	16.16	11.17–23.39	< 0.001
≥ 11	26 (2.0)	69 (27.0)	33.87	20.57–55.75	< 0.001
ETE					
No	1087 (85.3)	152 (59.4)	1.00		
Yes	188 (14.7)	104 (40.6)	3.96	2.95–5.30	< 0.001
Bilateral multifocality					
No	996 (78.1)	135 (52.7)	1.00		
Yes	279 (21.9)	121 (47.3)	3.20	2.42–4.23	< 0.001

Characteristic	Without ENE (N = 1275)	With ENE (N = 256)	Odds ratio	95% CI	<i>p</i> value
	No. (%)	No. (%)			
Abbreviations: PTC, papillary thyroid carcinoma; ENE, extranodal extension; ETE, extrathyroidal extension; CI, confidence interval.					

Five variables that retained significance upon multivariate analysis were men versus women (OR, 1.98; 95% CI, 1.37 to 2.87; $P < 0.001$), age 61 years or older versus age 31–60 years (OR, 1.93; 95% CI, 1.08 to 3.35; $P = 0.023$), having 6–10 positive nodes versus having 5 positive nodes or less (OR, 16.45; 95% CI, 11.07 to 24.68; $P < 0.001$), ETE versus no ETE (OR, 3.52; 95% CI, 2.42 to 5.14; $P < 0.001$), bilateral disease versus unilateral disease (OR, 2.18; 95% CI, 1.53 to 3.13; $P < 0.001$). Tumor size was not significantly associated with ENE in multivariate analysis (Table 3).

Table 3. Multivariate Logistic Regression Analysis of 1531 PTC Patients for Prediction of ENE						
	Full Model			Final Model		
	Odds ratio	95% CI	<i>p</i> value	Odds ratio	95% CI	<i>p</i> value
Gender						
Female	1.00			1.00		
Male	1.97	1.36 - 2.85	< 0.001	1.98	1.37 - 2.87	< 0.001
Age (years)						
31-60	1.00			1.00		
≤ 30	1.14	0.69 - 1.87	0.606	1.20	0.73 - 1.95	0.469
≥ 61	1.85	1.03 - 3.22	0.035	1.93	1.08 - 3.35	0.023
Tumor size (mm)						
≤ 20	1.00					
21 - 40	1.33	0.87 - 2.03	0.186			
≥ 41	1.55	0.67 - 3.43	0.294			
No. of positive nodes						
≤ 5	1.00			1.00		
6 - 10	15.90	10.68 - 23.90	< 0.001	16.45	11.07 - 24.68	< 0.001
≥ 11	26.69	15.65 - 46.69	< 0.001	28.31	16.74 - 49.17	< 0.001
ETE						
No	1.00			1.00		
Yes	3.20	2.15 - 4.76	< 0.001	3.52	2.42 - 5.14	< 0.001
Bilateral multifocality						
No	1.00			1.00		
Yes	2.16	1.51 - 3.10	< 0.001	2.18	1.53 - 3.13	< 0.001
Abbreviations: PTC, papillary thyroid carcinoma; ENE, extranodal extension; ETE, extrathyroidal extension; CI, confidence interval.						

Data of patients with T1-2 PTC were further analyzed. In multivariate analysis, sex, number of positive nodes, and bilateral multifocality still showed independent association with ENE (Table 4).

Table 4
Univariate and Multivariate Analysis of 1222 Patients With T1-2 PTC for Prediction of ENE

Univariate analysis				Multivariate analysis		
	Odds ratio	95% CI	<i>p</i> value	Odds ratio	95% CI	<i>p</i> value
Gender						
Female	1.00			1.00		
Male	1.96	1.35–2.81	< 0.001	1.94	1.25 to 3.02	0.003
Age (years)						
31–60	1.00					
≤ 30	1.41	0.86–2.24	0.159			
≥ 61	1.03	0.49–1.95	0.943			
Tumor size (mm)						
≤ 20	1.00			1.00		
21–40	2.25	1.45–3.41	< 0.001	1.57	0.91 to 2.64	0.096
No. of positive nodes						
≤ 5	1.00			1.00		
6–10	16.85	10.72 to 26.65	< 0.001	16.37	10.29 to 26.24	< 0.001
≥ 11	29.52	16.54 to 53.85	< 0.001	22.63	12.32 to 42.33	< 0.001
Bilateral multifocality						
No	1.00			1.00		
Yes	3.09	2.15 to 4.42	< 0.001	2.38	1.54 to 3.68	< 0.001
Abbreviations: PTC, papillary thyroid carcinoma; ENE, extranodal extension; CI, confidence interval.						

Discussion

There is a sex disparity in patients with papillary thyroid cancer. Men with thyroid cancer are more likely to have advanced disease and tumors with aggressive histological subtypes[7, 11]. This study examined the association between sex and the risk of ENE in PTC patients. Through multivariate analysis five variables were found to be associated with ENE, including male sex, ETE, older age, more positive nodes, and bilateral multifocality. Our results indicated male sex had a higher risk of ENE.

Lymph node metastasis is common in PTC patients. And some metastatic nodes may show ENE. Patients with ENE may have worse prognosis[15]. ENE is an independent variable associated with poor overall survival[4] and disease-specific survival[16]. The presence of ENE also increases the risk of recurrence[3, 17, 18, 4, 19]. ENE has a significant association with local recurrent disease[20, 21]. The presence of ENE in low volume LN metastasis indicates an intermediate risk of recurrence[2]. ENE is also associated with a lower probability of achieving an excellent response to initial therapy[20, 5].

Some clinical and pathological factors have been found to be associated with ENE in PTC. Kim et al[19] found that ETE, central and lateral neck involvement, lymph node ratio, and 3 positive nodes or more could predict ENE. Roh et al[4] found that sex, ETE, N1 classification, and number of positive nodes were all significant factors associated with occurrence of ENE. Other studies have demonstrated that large tumor size[22] and lymph node size[23] increase the risk of ENE for metastatic PTC.

Similar to previously reported studies[4, 22], in our study cohort men were associated with higher risk of ENE both in univariate and in multivariate analyses. Our results indicated male sex was an independent prognostic factor of ENE. Because ETE was also a risk factor of ENE, we further investigated the association between sex and ENE in patients with early-stage PTC. Multivariate analyses revealed that men were still independently associated with ENE in T1-2 PTC patients. In contrast, Kim et al[19] observed that male was a significant risk factor of ENE in univariate analyses, but not in the multivariate analyses after analyzing 1693 PTC patients. That might be due to the differences in population characteristics. In Kim et al's study, the median age was older (median age, 55 years), and up to 64.2% patients had ETE.

Our study has some limitations. First, this is a retrospective study using data from a single tertiary institution. The results need to be externally validated using data from other centers. Second, 67.7% of the patients in our series had papillary thyroid microcarcinoma, This might be due to increased use of thyroid cancer screening. Third, there was no follow-up data in our series. Though men were independently associated with ENE, the impacts of sex on survival and recurrence in PTC were not analyzed in our cohort study. However, these were out of scope of our study.

In summary, our analyses demonstrate that male sex, as well as older age, more positive nodes, ETE, and bilateral multifocality, is independently associated with ENE. Male sex has a higher risk of ENE in PTC. The potential mechanism needs to be further investigated.

Declarations

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Conflicts of interest: The authors have no relevant financial or non-financial interests to disclose.

Availability of data and material: The data that support the findings of this study are available on request from the corresponding author.

Code availability: Not applicable

Ethics approval: Ethical approval was waived by the local Ethics Committee of the Affiliated Cancer Hospital of Zhengzhou University in view of the retrospective nature of the study and all the procedures being performed were part of the routine care.

Consent to participate: Not applicable

Consent for publication: Not applicable

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Figures

Figure 1

Nonlinear continuous univariable effects of (A) tumor size, (B) number of positive nodes, and (C) age on extranodal extension. Shaded gray regions are 95% confidence bands.