Extranodal Extension Is an Independent Predictor of Lung Metastasis in Papillary Thyroid Cancer

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Research Article

Keywords: papillary thyroid cancer, extranodal extension, lung metastasis, lymph node

Posted Date: August 23rd, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-832567/v1>

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Abstract

Purpose

Lymph node metastasis is common in patients with papillary thyroid cancer (PTC). Some metastatic lymph nodes may present extranodal extension (ENE). The clinical role of ENE in PTC has yet to be clearly identified. We evaluated macroscopic ENE as a potential prognostic indicator of lung metastasis in PTC.

Patients and Methods

We identified 1140 consecutive patients who had PTC initially resected at our cancer center. Clinical data and pathological results were reviewed. Univariate and multivariate logistic regression analyses were used to figure out the association between clinicopathological variables and lung metastasis.

Results

In this cohort, 51.7% of PTC patients had lymph node metastasis; 10.4% had macroscopic ENE positive nodes; 2.3% had lung metastasis. In patients with lymph node metastasis, the average number of positive nodes was 5.10 ± 4.91 . Multivariable analysis of clinicopathological factors revealed that extrathyroidal extension (odds ratio [OR], 3.57; 95% CI, 1.41–9.04), macroscopic ENE (OR, 7.08; 95% CI, 2.54–19.74), and number of positive nodes were significantly associated with lung metastasis. Compared with 0–3 positive nodes, 7–9 positive nodes denoted a moderate risk of lung metastasis (OR, 4.53; 95% CI, 1.03–19.85). And 10 positive nodes or more indicated a high risk of lung metastasis (OR, 9.63; 95% CI, 2.65–35.02).

Conclusion

Macroscopic ENE could serve as a strong independent prognostic factor of lung metastasis in PTC. More attention should be paid to patients with ENE positive nodes during follow-up.

Introduction

Distant metastasis may occur in some patients with papillary thyroid cancer (PTC). Lung is the most common site of distant metastasis in PTC[1]. The incidence of lung metastasis is 2.1–8.1%[2–5]. Lung metastasis may lead to an upstaging of disease and indicates poor prognosis. Patients with lung metastasis often have shorter survival than those without[1]. And these patients always require more aggressive treatment, such as radioactive iodine therapy, and target therapy.

Tumor-related factors have been found to be associated with lung metastasis in PTC patients, including larger tumor size[3] and extrathyroidal extension (ETE)[6]. The association between lymph node metastasis and lung metastasis was also reported. Number of lymph node metastases[3], bilateral neck node metastases[5], and mediastinal lymph node metastasis[3] were associated with lung metastasis.

Lymph node metastasis is common in PTC patients. Some positive nodes may show more aggressive behavior, such as extranodal extension (ENE). The clinical role of ENE during PTC progression remains to be fully understood. In this analysis, we aim to determine the prognostic significance of macroscopic ENE on lung metastasis in PTC.

Patients And Methods

Patients and Database

This study was approved by Institutional Review Board of the Affiliated Cancer Hospital of Zhengzhou University. Medical records of 1242 consecutive PTC patients who underwent initial surgical resection between July 2012 and August 2014 were reviewed. Among these, 99 patients were excluded due to missing data. Three patients with distant metastasis but not lung (brain, 1; kidney, 1; sternum, 1) were also excluded. Finally, 1140 PTC patients were identified. Clinical and pathological data for each patient were collected for further analysis.

Tumor size was defined by the largest tumor diameter based on preoperative ultrasound report. Macroscopic ETE was identified during surgery, and was defined as local invasion of surrounding structures by primary tumor. Pathological T classification and N classification were defined according to the eighth edition of the American Joint Commission on Cancer (AJCC) TNM staging system[7]. ENE was defined as the extension of metastatic cells beyond the nodal capsule into the perinodal soft tissue[8]. Macroscopic ENE could be detected intraoperatively with the naked eyes. Lung metastasis was detected at time of diagnosis by preoperative chest X-ray or CT scan, and was confirmed by postoperative whole-body radioiodine scan. Bilateral multifocality and number of positive nodes were identified in the final pathology report.

Statistical Analysis

The association of macroscopic ENE with other clinical categorical variables was assessed using Fisher's exact test. And the association of macroscopic ENE with other continuous variables was assessed using analysis of variance. Nonlinear effects of continuous variables were tested by restricted cubic splines. When significant ($P < .05$) nonlinearity was found, the effect curve was plotted with 95% confidence bands for visual inspection. And this continuous variable would be transformed into a categorical variable for further analysis. The effect of macroscopic ENE on lung metastasis was analyzed using univariate and multivariate logistic regression. Odds ratio (OR) and 95% confidence interval (CI) were calculated. The variables that had statistically significant difference in multivariate logistic model were considered as independent prognostic variables.

Statistical analyses were conducted using R language (<http://www.r-project.org/>). All statistical tests were two tailed, and results were considered significant at $p < .05$.

Results

The study cohort consisted of 1140 PTC patients, with mean age 44.85 ± 11.83 years (range, 10 to 77 years), and with mean tumor size 15.58 ± 11.55 mm. Of the 1140 patients, 848 (74.4%) were female, 222 (19.5%) with macroscopic ETE, 295 (25.9%) with bilateral multifocality, and 118 (10.4%) with macroscopic ENE. Of these, 373 (32.7%) patients had N1b disease, and 26 (2.3%) had lung metastasis. Patient characteristics and clinicopathological variables are listed in Table 1.

Table 1

Demographic and Tumor Characteristics of 1140 PTC Patients With and Without Macroscopic Extranodal Extension

Characteristic	All patients	Without macroscopic ENE	With macroscopic ENE	<i>p</i> value
	No. (%)	No. (%)	No. (%)	
Total No. of patients	1140 (100)	1022 (89.6)	118 (10.4)	
Gender				< 0.001*
Female	848 (74.4)	776 (75.9)	72 (61.0)	
Male	292 (25.6)	246 (24.1)	46 (39.0)	
Age (years)				
Mean ± SD	44.85 ± 11.83	44.75 ± 11.50	45.79 ± 14.39	0.365†
Tumor size (mm)				
Mean ± SD	15.58 ± 11.55	14.57 ± 10.79	24.29 ± 14.03	< 0.001†
No. of positive nodes				
Mean ± SD	2.63 ± 4.35	1.94 ± 3.42	8.61 ± 6.48	< 0.001†
Macroscopic ETE				< 0.001*
No	918 (80.5)	865 (84.6)	53 (44.9)	
Yes	222 (19.5)	157 (15.4)	65 (55.1)	
Bilateral multifocality				< 0.001*
No	845 (74.1)	786 (76.9)	59 (50.0)	
Yes	295 (25.9)	236 (23.1)	59 (50.0)	
Pathological T classification				< 0.001*
T1	759 (66.6)	725 (70.9)	34 (28.8)	
T2	138 (12.1)	121 (11.8)	17 (14.4)	
T3	111 (9.7)	92 (9.0)	19 (16.1)	

Characteristic	All patients	Without macroscopic ENE	With macroscopic ENE	<i>p</i> value
	No. (%)	No. (%)	No. (%)	
T4	132 (11.6)	84 (8.2)	48 (40.7)	
Pathological N classification				< 0.001*
N0	551 (48.3)	551 (53.9)	0 (0)	
N1a	216 (18.9)	206 (20.2)	10 (8.5)	
N1b	373 (32.7)	265 (25.9)	108 (91.5)	
M classification				< 0.001*
M0	1114 (97.7)	1015 (99.3)	99 (83.9)	
M1	26 (2.3)	7 (0.7)	19 (16.1)	
Abbreviations: PTC, papillary thyroid carcinoma; ENE, extranodal extension; ETE, extrathyroidal extension; SD, standard deviation.				
*Fisher's exact test was used. †Analysis of variance (ANOVA) was used.				

ENE-positive rate was correlated with other clinicopathological factors in PTC. In our cohort, larger tumor size, male, more positive nodes, macroscopic ETE, bilateral multifocality, advanced T classification, and advanced N classification, were all associated with macroscopic ENE. Age was not associated with macroscopic ENE (Table 1).

The association of macroscopic ENE as well as other clinicopathological factors with lung metastasis was investigated by univariate logistic regression analyses (Table 2). In our series, tumor size was associated with lung metastasis ($P = .004$). The risk of lung metastasis was found to increase with tumor size in a nonlinear fashion (Fig. 1A). Number of positive nodes was also significantly associated with lung metastasis ($P = .002$), with a higher risk of lung metastasis for patients with more positive nodes according to a nonlinear function (Fig. 1B). So tumor size and number of positive nodes were transformed into categorical variables for analysis. Another strong predictor of lung metastasis was macroscopic ENE. The lung metastasis rate was 27.83-fold greater for patients with macroscopic ENE-positive nodes versus patients with macroscopic ENE-negative nodes (19.2% v 0.7%, respectively; $P < .001$). The other variables, including macroscopic ETE, bilateral multifocality, and pathological T classification, were also significantly associated with lung metastasis. Gender and age were not associated with lung metastasis.

Table 2
Univariate Association Between Lung Metastasis and Clinicopathological Characteristics in 1140 PTC Patients

Characteristic	Without Lung Metastasis (N = 1114)	With Lung Metastasis (N = 26)	Odds ratio	95% CI	<i>p</i> value
	No. (%)	No. (%)			
Gender					
Female	830 (74.5)	18 (69.2)	1.00		
Male	284 (25.5)	8 (30.8)	1.30	0.56–3.02	0.543
Age (years)					
Mean ± SD	44.85 ± 11.77	44.73 ± 14.22	1.00	0.97–1.03	0.957
Tumor size (mm)					
≤10	565 (50.7)	2 (7.7)	1.00		
11–20	315 (28.3)	5 (19.2)	4.48	0.86–23.25	0.074
21–30	145 (13.0)	7 (26.9)	13.64	2.80–66.34	0.001
31–40	54 (4.8)	7 (26.9)	36.62	7.42–180.67	< 0.001
≥41	35 (3.1)	5 (19.2)	40.36	7.56–215.45	< 0.001
No. of positive nodes					
≤3	850 (76.3)	4 (15.4)	1.00		
4–6	123 (11.0)	4 (15.4)	6.91	1.71–27.99	0.007
7–9	67 (6.0)	5 (19.2)	15.86	4.16–60.45	< 0.001
≥10	74 (6.6)	13 (50.0)	37.33	11.87–117.38	< 0.001
Macroscopic ETE					
No	910 (81.7)	8 (30.8)	1.00		
Yes	204 (18.3)	18 (69.2)	10.04	4.30–23.40	< 0.001
Bilateral multifocality					

Characteristic	Without Lung Metastasis (N = 1114)	With Lung Metastasis (N = 26)	Odds ratio	95% CI	<i>p</i> value
	No. (%)	No. (%)			
No	833 (74.8)	12 (46.2)	1.00		
Yes	281 (25.2)	14 (53.8)	3.46	1.58–7.57	0.002
Pathological T classification					
T1	755 (67.8)	4 (15.4)	1.00		
T2	135 (12.1)	3 (11.5)	4.19	0.93–18.95	0.062
T3	106 (9.5)	5 (19.2)	8.90	2.35–33.68	0.001
T4	118 (10.6)	14 (53.8)	22.39	7.25–69.19	< 0.001
Macroscopic ENE					
No	1015 (91.1)	7 (26.9)	1.00		
Yes	99 (8.9)	19 (73.1)	27.83	11.42–67.82	< 0.001
Abbreviations: PTC, papillary thyroid carcinoma; ENE, extranodal extension; ETE, extrathyroidal extension; SD, standard deviation; CI, confidence interval.					

Multivariate models are shown in Table 3. In the final multivariate model, number of positive nodes, macroscopic ETE, and macroscopic ENE were significantly and independently associated with an increased likelihood of lung metastasis. Patients with 7–9 positive nodes were 4.53 fold greater to have lung metastasis than patients with 3 positive nodes or less. Patients with macroscopic ENE-positive nodes were 7.08-fold greater to have lung metastasis than patients with macroscopic ENE-negative nodes.

Table 3
Multivariate Logistic Regression Analysis of 1140 PTC Patients for Prediction of Lung Metastasis

Full Model				Final Model		
	Odds ratio	95% CI	<i>p</i> value	Odds ratio	95% CI	<i>p</i> value
Tumor size (mm)						
=<10	1.00					
11–20	1.96	0.33–11.67	0.457			
21–30	4.49	0.61–33.17	0.141			
31–40	8.03	1.00–64.16	0.049			
>=41	8.47	0.95–75.58	0.056			
No. of positive nodes						
=<3	1.00			1.00		
4–6	2.07	0.45–9.56	0.351	2.64	0.59–11.74	0.201
7–9	2.69	0.56–12.93	0.217	4.53	1.03–19.85	0.045
>=10	6.02	1.52–23.90	0.011	9.63	2.65–35.02	< 0.001
Macroscopic ETE						
No	1.00			1.00		
Yes	1.63	0.12–22.39	0.713	3.57	1.41–9.04	0.007
Bilateral multifocality						
No	1.00					
Yes	1.05	0.41–2.66	0.917			
Pathological T classification						
T1	1.00					
T2	0.48	0.07–3.37	0.463			

	Full Model			Final Model		
T3	0.85	0.05– 13.66	0.906			
T4	1.18	0.05– 27.98	0.919			
Macroscopic ENE						
No	1.00			1.00		
Yes	7.37	2.55– 21.31	< 0.001	7.08	2.54– 19.74	< 0.001
Abbreviations: PTC, papillary thyroid carcinoma; ENE, extranodal extension; ETE, extrathyroidal extension; CI, confidence interval.						

Discussion

In this study, the association between macroscopic ENE and lung metastasis in PTC was investigated. Macroscopic ENE was found in 10.4% of PTC patients, and lung metastasis was found in 2.3% of patients. Macroscopic ENE and lung metastasis rates were similar to the published literature[9–11, 4]. After multivariate logistic regression analysis, macroscopic ENE, macroscopic ETE and number of positive nodes showed association with lung metastasis, which indicated the independent predictive value. Patients with macroscopic ENE positive nodes were seven-fold greater to have lung metastasis than patients with macroscopic ENE-negative nodes. This further supports a role for macroscopic ENE not just in regional lymph node metastasis, but also in distant metastasis.

Lymph node metastasis is common in PTC patients. The clinical significance of lymph node metastasis had been widely studied. These studies focused on different aspects of metastatic nodes, including, but not limited to, anatomical location[12], number[13, 3], maximum size[14, 15, 13], and ratio of positive nodes[16, 17].

ENE has become an understudied aspect of lymph node metastasis in PTC. The clinical significance of ENE in PTC patients remains to be explored. The utility of ENE to clinicians still continues to be debated. Previous studies have suggested a significant correlation between ENE in PTC and higher risk of recurrence[18, 10, 11, 19–21, 8]. ENE was also associated with compromised survival in PTC patients[10, 22, 23], and was an independent risk factor for nonexcellent response to initial therapy[24, 25]. ENE was proposed as an prognostic value to upstage the TNM staging for ENE-positive PTC patients[26].

Some advanced PTC patients may have distant metastasis. Lung is the most common site of distant metastasis. Lung metastasis predicts shorter disease-specific survival of PTC patients[27, 28]. Some clinicopathological factors were found to be correlated with lung metastasis, such as number of metastatic nodes[3], bilateral lateral cervical lymph node metastasis[4, 5], and ETE[6]. In our series,

number of positive nodes and macroscopic ETE were also found to be independent prognostic risk factors of lung metastasis.

The association between ENE and lung metastasis was rarely reported. In our study, we show that macroscopic ENE is associated with increased likelihood of lung metastasis on multivariate analysis. Therefore, macroscopic ENE is an independent predictor of lung metastasis, indicating a role for ENE in PTC dissemination. Our results reinforce findings of other studies. In Lee's study, ENE and age 45 years or older were risk factors for distant metastasis[29]. In Jeon's study, ENE and aggressive pathologic subtype of metastatic nodes could help to assess the risk of distant metastasis in patients with papillary thyroid microcarcinoma[30].

Our study has some limitations. First, this is a retrospective study from a single institution. The results need to be validated in prospective studies. Second, though macroscopic ENE is associated with lung metastasis in our series, the association between macroscopic ENE and tumor prognosis needs to be investigated further. Third, there are no long-term follow-up data in our series, so metachronous lung metastasis was not included. Four, lung metastases in this study were only clinically evaluated, and there was a lack of surgical and pathological evaluations.

In conclusion, our data suggest that macroscopic ENE, macroscopic ETE, and number of positive nodes are independent risk factors of lung metastasis in PTC. Macroscopic ENE may be used as a stratification tool to assess the risk of distant metastasis in PTC patients. Further investigations are needed to figure out the clinical utility of ENE.

Declarations

Funding: This study was funded by Henan Health Commission (grant number 2018020490).

Conflicts of Interest: The authors declare that they have no conflict of interest.

Availability of data and material: The datasets generated analyzed during the current study are available from the corresponding author on reasonable request.

Code availability: Not applicable.

Authors' contributions: HH and JWQ designed research; HH, WBG, and CZ conducted research; HH and BZ analyzed data; HH wrote the paper; JWQ had primary responsibility for final content. All authors read and approved the final manuscript.

Ethics approval and consent to participate: The study was reviewed and approved by Institutional Review Board of the Affiliated Cancer Hospital of Zhengzhou University. This study was conducted in accordance with the Declaration of Helsinki.

Consent for publication: All authors have reviewed the final version of the manuscript and are in agreement its content and submission.

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Figures

Figure 1

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