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Original Article

Association of maximum tumor diameter with the metastatic number of lymph node in papillary thyroid cancer

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Abstract: Purpose: The relationship between the maximum tumor diameters (MTD) with the number of metastatic lymph nodes in papillary thyroid cancer (PTC) remains unclear. Thus, this study aimed to investigate the association of MTD with the number of metastatic lymph nodes in PTC. Methods: Total 1389 patients with PTC who underwent total thyroidectomy and central lymph node dissection were analyzed. Univariate and multivariate logistic regression models were used to assess whether the MTD and other covariates had independent effects on the number of metastatic lymph nodes. Results: Lymph node metastases (LNM) were found more frequently in the MTD > 1 cm group than in the MTD ≤ 1 cm group ($P < 0.001$). Univariate regression analysis showed that MTD was significantly correlated with the number of metastatic lymph nodes (odds ratio [OR] = 4.0, 95% confidence interval [CI] = 3.6-4.4; $P < 0.001$). After multivariable risk adjustment for potential confounding factors, MTD, subtype, extrathyroid extension, infiltration, and multifocality were found to be independently and positively associated with the number of metastatic lymph nodes. A linear relationship between the MTD and the number of metastatic lymph nodes was observed. Conclusions: Our findings suggest that MTD is associated with metastatic number of lymph node in PTMCs. Radical treatment may be necessary for larger MTD patients.

Keywords: Maximum tumor diameter, metastatic number of lymph node, papillary thyroid cancer

Introduction

The incidence of papillary thyroid cancer (PTC) is increasing more quickly than that of any other malignancy in the United States and China [1-4]. Among women, thyroid cancer is the most commonly diagnosed cancer before the age of 30 years [3]. The dramatic rise in thyroid cancer among women in China is consistent with that observed in other countries [5]. The increasing incidence of PTC, especially papillary thyroid microcarcinoma, is partly due to the increased accuracy of pathologic thyroid examination, in particular the thinness and the number of the anatomical slices obtained from thyroid specimens [6, 7].

A recent report from the Surveillance, Epidemiology, and End Results (SEER) program showed that lymph node metastases were associated with increased mortality in patients with differentiated thyroid cancer [8]. In the current American Joint Committee on Cancer (AJCC) staging system, the number of metastatic lymph nodes has been proven to be a prognostic factor in PTC [9, 10]; however, additional knowledge about the predictors of the number of metastatic lymph nodes in PTC is required.

Clinicopathological risk factors for lymph node metastasis (LNM) in PTC have been reported in recent studies to include extrathyroid extension (ETE), multifocal disease, larger tumor diameter, age at diagnosis of less than 45 years, and male sex, among others [11-14]. However, whether these risk factors are associated with the number of metastatic lymph node remains unclear. Therefore, in this study, we aimed to investigate the association of maximum tumor diameter (MTD) with the number of metastatic lymph nodes in PTC.

Materials and methods

Patients

A total of 1389 consecutive patients with PTC who underwent total-thyroidectomy plus cen-

Table 1. Demographic and clinical characteristics of the cases included in the study

Characteristics	MTD ≤ 1 cm	MTD > 1 cm	*P*-value
Age (years)			< 0.0001
< 45	419 (64.66%)	229 (35.34%)	
≥ 45	554 (74.76%)	187 (25.24%)	
Sex			0.0009
Female	802 (72.01%)	312 (27.98%)	
Male	170 (61.82%)	105 (38.18%)	
LNM			< 0.0001
Absent	716 (84.93%)	127 (15.07%)	
Present	257 (47.07%)	289 (52.93%)	
Subtype			< 0.0001
Classic	901 (68.67%)	411 (31.33%)	
Other types	72 (93.51%)	5 (6.49%)	
ETE			< 0.0001
Absent	719 (79.89%)	181 (20.11%)	
Present	254 (51.94%)	235 (48.06%)	
Infiltration			< 0.0001
Absent	942 (72.69%)	354 (27.31%)	
Present	31 (33.33%)	62 (66.67%)	
Multifocal			0.0011
Absent	626 (73.22%)	229 (26.78%)	
Present	347 (64.98%)	187 (35.02%)	
Hashimoto			0.0025
Absent	691 (67.81%)	328 (32.19%)	
Present	282 (76.22%)	88 (23.78%)	

MTD: maximum tumor diameter, ETE: extrathyroid extension, LNM: lymph node metastasis.

tral lymph node dissection at our hospital between January 2001 and December 2015 were included for analysis. Clinical and surgical data for the cases reviewed were obtained from our clinical database, and the study protocol was approved by our institutional review board (Jingmen First people's Hospital Ethics Committee), and written informed consent was obtained from each patient.

Surgical technique and pathological confirmation

Total thyroidectomy associated with bilateral central neck dissection were performed for patients diagnosed with malignancy, regardless of age, six, diameter, foci number and disease stage. Fine-needle aspiration biopsy (FNAB) and/or intraoperative frozen section examination is routinely performed during a thyroid surgical procedure. Routine pathological examination was performed by two experienced pathologists. MTD was defined to be the dominant tumor's largest diameter of PTCs.

Statistical analysis

The data distribution of each covariate between the MTD ≤ 1 cm and the MTD > 1 cm groups were first compared, using the t test (normal distribution) for continuous variables and x^2 tests for categorical data. Next, univariate logistic regression, stratified analysis and multivariate logistic regression models were used to examine whether MTD and other covariates had an independent effect on metastatic number of lymph node separately. The two-way ANOVA analysis was used to analyze the value of MTD and multifocality in PTCs. Then we explored the relationship between MTD and metastatic number of lymph node by the smoothing plot, with an adjustment for potential confounders. All data were double entered and then exported to tab-delimited text files. All analyses were performed with EmpowerStats software (www.empowerstats.com, X&Y solutions, Inc. Boston MA).

Results

Among the 1389 patients included in the study, there were 973 (70.1%) and 416 (29.9%) with the MTD ≤ 1 cm and MTD > 1 cm, respectively. The demographic and clinical characteristics of the analyzed cases including age, sex, LNM, subtype, ETE, infiltration, multifocal and combined with Hashimoto, are summarized in **Table 1**. Of note, LNM were found more frequently in the MTD > 1 cm group than in the MTD ≤ 1 cm group (P < 0.001). In addition, age < 45 years, male, multifocality, classic subtype, extrathyroid extension, infiltration, multifocal and combined Hashimoto were more common in the MTD > 1 cm group.

Univariate regression analysis showed that MTD was significantly correlated with the number of metastatic lymph nodes (odds ratio [OR] = 4.0, 95% confidence interval [CI] = 3.6-4.4, P < 0.001). In addition, subtype (OR = -1.4, 95% CI = -2.3--0.5, P = 0.003), ETE (OR = 1.5, 95% CI = 1.1-2.0, P < 0.001), infiltration (OR = 2.0, 95% CI = 1.2-2.9, P < 0.001), multifocal (OR = 1.0, 95% CI = 0.6-1.4, P < 0.001), age (OR = -1.6, 95% CI = -2.0-1.2, P < 0.001), sex (OR = 1.3, 95% CI = 0.7-1.8, P < 0.001) also associated with the number of metastatic lymph

Table 2. Effects of risk factors on LNM number by univariate analysis

	Statistics	Odds ratio (95% CI)	*P* value
MTD (cm)			
≤ 1	973 (70.1%)	0	
> 1	416 (29.9%)	4.0 (3.6, 4.4)	< 0.001
Subtype			
Classic	1312 (94.5%)	0	
Other types	77 (5.5%)	-1.4 (-2.3, -0.5)	0.003
ETE			
Absent	900 (64.8%)	0	
Present	489 (35.2%)	1.5 (1.1, 2.0)	< 0.001
Infiltration			
Present	1296 (93.3%)	0	
Absent	93 (6.7%)	2.0 (1.2, 2.9)	< 0.001
Multifocal			
Absent	855 (61.6%)	0	
Present	534 (38.4%)	1.0 (0.6, 1.4)	< 0.001
Hashimoto			
Absent	1019 (73.4%)	0	
Present	370 (26.6%)	-0.2 (-0.7, 0.3)	0.353
Age(years)			
< 45	648 (46.7%)	0	
≥ 45	741 (53.3%)	-1.6 (-2.0, -1.2)	< 0.001
Sex			
Female	1113 (80.2%)	0	
Male	275 (19.8%)	1.3 (0.7, 1.8)	< 0.001

MTD: maximum tumor diameter, ETE: extrathyroid extension, LNM: lymph node metastasis.

Table 3. Effects of risk factors on LNM number by stratified analysis

	N	Odds ratio (95% CI)	*P* value
MTD			
Age (years)			
< 45	648	4.8 (4.1, 5.5)	< 0.0001
≥ 45	741	2.8 (2.4, 3.3)	< 0.0001
Sex			
Female	1113	3.5 (3.0, 3.9)	< 0.0001
Male	275	5.5 (4.4, 6.5)	< 0.0001
BMI Tertile			
Low	463	4.5 (3.7, 5.3)	< 0.0001
Middle	463	3.5 (2.9, 4.1)	< 0.0001
High	463	4.1 (3.4, 4.9)	< 0.0001

MTD: maximum tumor diameter; BMI: body mass index.

nodes (**Table 2**). The stratified analysis suggested that MTD had a positive correlation with the number of metastatic lymph nodes both in patients ≥ 45 years old and < 45 years old, female and male, and low, middle and high BMI group (**Table 3**). After multivariable risk adjustment for potential confounding factors (**Table 4**), MTD, Subtype, ETE, infiltration and multifocal were found to be independently and positively associated with the number of metastatic lymph nodes.

Finally, we found that MTD was obviously correlated with the multifocality (P < 0.001) (**Figure 1**). After adjusting for these possible factors related to the number of metastatic lymph nodes including age, sex, BMI, extrathyroid extension, infiltration, multifocility, and combined Hashimoto, a linear relationship between MTD and the number of metastatic lymph nodes was observed (**Figure 2**). The number of LNMs increased with increasing in these patients with MTD level < 2.4 cm (OR = 2.7, 95% CI = 2.4-3.0; P < 0.001) and with MTD level > 2.4 cm (OR = 1.2, 95% CI = 0.4-2.0; P = 0.003) (**Table 5**).

Discussion

Although PTC is a relatively indolent disease and patients usually enjoy a good prognosis, it does have a risk for LNM and local recurrence [15, 16]. Recurrence and persistent disease demand additional therapy and can affect the PTC patients' quality of life. For example, recurrence increases the risk of reoperations and the exposure to a high cumulative radioiodine dose [17]. LNM at the time of initial operation were significantly related to postoperative recurrence, and follow-up supervision must be enhanced after initial treatment to mitigate PTC recurrence in these susceptible patients [18, 19].

It has been recently reported that the number of metastatic lymph nodes may be a statistical significant predictive factor associated with disease recurrence [16, 20, 21]. Lee *et al*. found that the number of metastatic lymph nodes was a significant prognostic factor and demonstrated that the significance of the number of metastatic lymph nodes in risk stratification for recurrence in PTC. Total thyroidectomy and radioactive iodine therapy may benefit for patients with ≥ 2 metastatic lymph nodes [17]. In the latest American Joint Committee on Cancer staging system, the concept of the number of metastatic lymph nodes was also men-

Table 4. Multivariate logistic regression model for risk factors associated with LNM number

	Non-adjusted	Adjust I	Adjust II
MTD	4.0 (3.6, 4.4) < 0.0001	3.8 (3.4, 4.2) < 0.0001	3.8 (3.4, 4.2) < 0.0001
Subtype	-1.4 (-2.3, -0.5) 0.0032	-1.1 (-2.0, -0.2) 0.0150	-1.1 (-2.0, -0.2) 0.0207
ETE	1.5 (1.1, 2.0) < 0.0001	1.5 (1.1, 1.9) < 0.0001	1.5 (1.0, 1.9) < 0.0001
Infiltration	2.0 (1.2, 2.9) < 0.0001	2.3 (1.5, 3.1) < 0.0001	2.3 (1.4, 3.1) < 0.0001
Multifocal	1.0 (0.6, 1.4) < 0.0001	0.9 (0.5, 1.4) < 0.0001	0.9 (0.5, 1.3) < 0.0001
Hashimoto	-0.2 (-0.7, 0.3) 0.3528	-0.2 (-0.7, 0.3) 0.4424	-0.2 (-0.7, 0.3) 0.4544

MTD: maximum tumor diameter, ETE: extrathyroid extension, LNM: lymph node metastasis. Odds ratios were derived from multivariate logistic regression analysis. Adjust I adjust for: AGE12; SEX; BMI; Adjust II adjust for: AGE12; SEX; BMI (smooth).

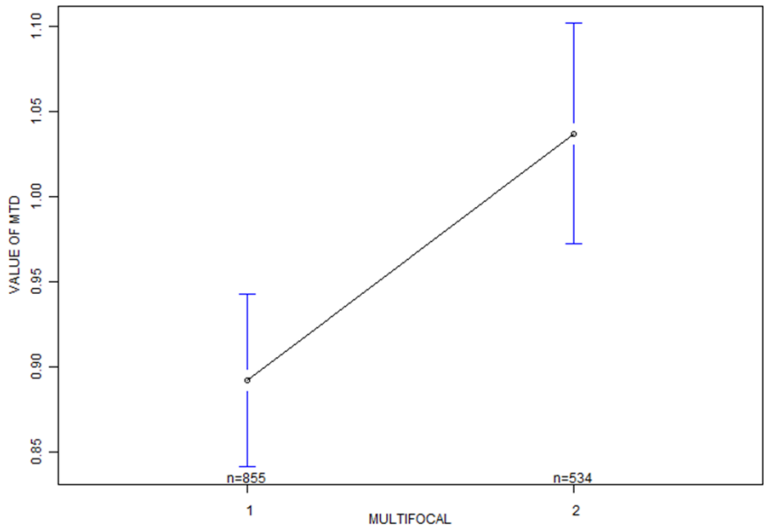

Figure 1. Correlation between value of MTD and multifocality by two-way ANOVA analysis. There was an obvious interaction between value of MTD and multifocality (P < 0.001).

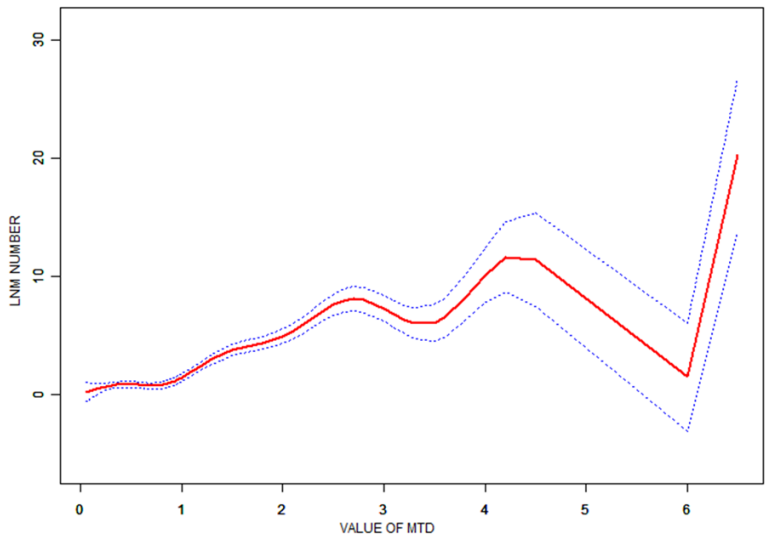

Figure 2. The relationship between the value of MTD and metastatic number of lymph nodes. A linear relationship between the value of MTD and metastatic number of lymph nodes was observed after adjusting for age, sex, BMI, extrathyroid extension, infiltration, multifocility, and combined Hashimoto. MTD: maximum tumor diameter.

tioned as an important factor for clinicians when deciding on the need for radical treatment such as completion thyroidectomy, further complete central lymph node dissection, or postoperative radioactive iodine treatment.

In other hand, the impact of the number of metastatic lymph nodes or threshold lymph node ratio (metastatic lymph nodes to total lymph nodes removed) on survival has also been defined. Adam *et al.* also suggested that there was a significant overall association between the risk of death and the number of metastatic lymph nodes; an increasing number of metastatic cervical lymph nodes was associated with decreasing survival for up to six metastatic lymph nodes for patients younger than age 45 years with stage I papillary thyroid cancer [16]. This afforded us the ability to perform multivariable adjustment for important factors such as extent of surgical resection and radioactive iodine therapy for these patients. Schneider *et al.* showed that lymph node ratio (LNR) is a strong determinant of disease-specific mortality and a threshold LNR of 0.42 can be used to risk-stratify patients with metastatic lymph nodes [22]. Therefore,

Table 5. Threshold effect analysis of MTD on metastatic number of lymph nodes using piecewise linear regression

Outcome	β (95% CI)	*P* value
Turning point (K): 2.4		
< K	2.7 (2.4, 3.0)	< 0.001
> K	1.2 (0.4, 2.0)	0.003

MTD: maximum tumor diameter.

investigating the risk factors for the number of metastatic lymph nodes may be with high clinical significance.

Conclusions of studies investigating the clinical and pathologic features predictive of lymph node metastasis have varied [12, 14]. Since tumor diameter such as MTD plays an important role in the TNM system, it was clinically important for us to study the association of MTD with the number of metastatic lymph nodes in PTC. In our study, univariate regression analysis showed that MTD was significantly correlated with the number of metastatic lymph nodes.

An MTD greater than 3 cm has been reported to be one of the risk factors for recurrence in the lymph nodes of papillary thyroid cancer [23, 24]. In our study, we demonstrated that MTD, subtype, ETE, infiltration, and multifocality were independently and positively associated with the number of metastatic lymph nodes after multivariable risk adjustment for potential confounding factors. In addition, to minimize the confounding effects of the primary tumor and to exclusively focus on MTD, a linear relationship between the MTD and the number of metastatic lymph nodes was observed. The number of LNMs increased with increasing MTD, in particular dramatically increasing when MTD was less than 2.4 cm and increasing more slowly when MTD was greater than 2.4 cm.

There are some limitations to our study. The first is that all PTC patients were collected from a single institution, which might result in selection bias and thereby weaken the study's statistical power. Second, not all lymph node dissections were complete lateral neck dissections; therefore, the rate of lymph node metastasis may be underrepresented due to incomplete histologic evaluation of regional lymph nodes in all PTCs. In addition, the data analyzed in this study were lacking follow-up data; therefore, we could not evaluate the effects of MTD on the outcomes of patients with PTCs.

In conclusion, our findings demonstrated that MTD is associated with the number of metastatic lymph node in PTC. Thus, taking MTD into consideration may help direct the diagnosis and treatment decisions for PTC.

Disclosure of conflict of interest

None.

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