Int J Clin Exp Med 2017;10(7):11197-11203
www.ijcem.com /ISSN:1940-5901/IJCEM0053517

Original Article

Effects of total tumor diameter on the metastatic number of lymph node in papillary thyroid microcarcinoma

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Received February 24, 2017; Accepted July 3, 2017; Epub July 15, 2017; Published July 30, 2017

Abstract: Purpose: Whether total tumor diameter (TTD) are associated with the number of metastatic lymph nodes in papillary thyroid microcarcinoma (PTMC) remains unclear. Thus, this study aimed to investigate the effects of TTD on the number of metastatic lymph nodes in PTMC. Methods: A series of 1106 patients with PTMC who underwent total-thyroidectomy plus central lymph node dissection were analyzed. The clinical correlation between the metastatic number of lymph node and TTD was retrospectively studied after adjusting for potential confounders. Univariate and multivariate logistic regression models were used to assess whether TTD and other covariates had independent effects on the number of metastatic lymph nodes. The relationship between TTD and the number of metastatic lymph nodes was subsequently explored using a smoothing plot. Results: Univariate regression analysis showed that TTD was significantly correlated with the number of metastatic lymph nodes (OR 0.2, 95% CI 0.0-0.4, P=0.045). In addition, subtype (OR -0.5, 95% CI -0.8 - -0.1, P=0.013), ETE (OR 0.4, 95% CI 0.1-0.6, P=0.002), infiltration (OR 0.9, 95% CI 0.3-1.4, P=0.003), age (OR -0.6, 95% CI -0.8 - -0.4, P<0.001), sex (OR 0.4, 95% CI 0.1-0.6, P=0.012) also associated with the number of metastatic lymph nodes. After multivariable risk adjustment for potential confounding factors, TTD, Subtype, ETE and infiltration were found to be positively associated with the number of metastatic lymph nodes. A linear relationship below the turning point (TTD<1 cm) between TTD and metastatic number of lymph node was observed. The number of LNMs increased with increasing TTD level when below the turning point (TTD<1 cm) (OR 1.0, 95% CI 0.6-1.4; P<0.001). Conclusions: Our findings suggest that TTD is associated with the metastatic number of lymph node in PTMCs. Radical treatment may be necessary for larger TTD patients.

Keywords: Total tumor diameter, metastatic number of lymph node, papillary thyroid microcarcinoma

Introduction

Papillary thyroid microcarcinoma (PTMC) is defined as papillary thyroid carcinoma measuring less or equal 1.0 cm in its greatest dimension according to the World Health Organization classification system [1, 2]. Several reports have described dramatic increases over recent decades in the incidence of PTMC partly owing to the increased accuracy of the pathologic thyroid examination, in particular due to the thinness and the number of the anatomical slices obtained for thyroid specimens [3-7].

AJCC classification system along with the guidelines recommended by the ATA defines the tumor size as traditional intraglandular maximal tumor diameter, whether the subgroup of multifocality in PTMC with (TTD)>1 cm has the same features of clinicopathological risk factors with traditional PTMCs are still unclear.

The number of metastatic lymph node and the ratio between the number of metastatic lymph node and the harvested lymph nodes have been proven to be a predictor for prognosis in PTMC [8-10]. Therefore, better knowledge about the predictors for number of metastatic lymph node in PTMC is required. In our study, our aim is to demonstrate whether TTD has effect on number of metastatic lymph node in PTMC.

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

Characteristics	TTD≤0.5 cm	0.5<TTD≤1 cm	1<TTD≤2 cm	TTD>2 cm	*P*-value
Age (years)					0.8430
<45	185 (39.7%)	207 (44.42%)	64 (13.73%)	10 (2.15%)	
≥45	270 (42.19%)	276 (43.12%)	80 (12.50%)	14 (2.19%)	
Sex					0.2726
Female	383 (41.54%)	406 (44.03%)	116 (12.58%)	17 (1.84%)	
Male	72 (39.13%)	77 (41.85%)	28 (15.22%)	7 (3.80%)	
LNM					0.0017
Absent	363 (44.11%)	338 (41.07%)	108 (13.12%)	14 (1.70%)	
Present	92 (32.51%)	145 (51.24%)	36 (12.72%)	10 (3.53%)	
Subtype					0.6291
Classic	423 (41.51%)	445 (43.67%)	129 (12.66%)	22 (2.16%)	
Other types	32 (36.78%)	38 (43.68%)	15 (17.24%)	2 (2.30%)	
ETE					0.8004
Absent	342 (41.91%)	352 (43.14%)	106 (12.99%)	16 (1.96%)	
Present	113 (38.97%)	131 (45.17%)	38 (13.1%)	8 (2.76%)	
Infiltration					0.4975
Absent	442 (41.42%)	461 (43.21%)	140 (13.12%)	24 (2.25%)	
Present	13 (33.33%)	22 (56.41%)	4 (10.26%)	0 (0.00%)	
Multifocal					<0.0001
Absent	392 (54.67%)	320 (44.63%)	4 (0.56%)	1 (0.14%)	
Present	63 (16.2%)	163 (41.9%)	140 (35.99%)	23 (5.91%)	
Hashimoto					0.7864
Absent	325 (41.09%)	345 (43.62%)	100 (12.64%)	21 (2.65%)	
Present	130 (41.27%)	138 (43.81%)	44 (13.97%)	3 (0.95%)	

TTD: total tumor diameter, ETE: extrathyroid extension, LNM: lymph node metastasis.

Materials and methods

A total of 1106 consecutive patients with PTMC who underwent total-thyroidectomy plus central lymph node dissection at union hospital between January 2003 and December 2014 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 (Union Hospital Ethics Committee), and written informed consent was obtained from each patient.

Surgical strategy and pathological confirmation

We performed total thyroidectomy associated with bilateral central neck dissection for patients diagnosed with malignancy, regardless of size, foci number and disease stage. Fine-needle aspiration biopsy (FNAB) and/or intraoperative frozen section examination is routinely performed during a thyroid surgical procedure. False-negative cases who had lobectomy and in whom were found more than one microcarcinoma foci by routine pathology would have residual thyroid resection with central lymph node dissection. Routine pathological examination was performed on the whole specimen with serial sectioning at 3-um intervals for hematoxylin and eosin staining, then diagnosed by two experienced pathologists according to the criteria of the World Health Organization. TTD was defined to be the largest diameter of dominant tumor for unifocal and of tumor for multifocal lesions in PTMCs.

Statistical analysis

We first compared the data distribution of each covariate between the less TTD and the larger TTD groups, using the t test (normal distribution) or Kruskal-Wallis rank sum test (non-normal distribution) for continuous variables and x^2 tests for categorical data (**Table 1**). Next, univariate logistic regression (**Table 2**), stratified analysis (**Table 3**) and multivariate logistic regression models (**Table 4**) were used to examine whether TTD and other covariates had an independent effect on metastatic number of lymph node separately. The two-way ANOVA analysis was used to analyze the distribution of TTD and tumor foci in PTMCs. Then we explored the relationship between TTD and metastatic number of lymph node by the Curve fitting, with an adjustment for potential con-

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

	Statistics	Odds ratio (95% CI)	*p* value
TTD (cm)			
≤0.5	455 (41.1%)	0	
0.5<TTD≤1	483 (43.7%)	0.2 (0.0, 0.4)	0.045
1<TTD≤2	144 (13.0%)	0.1 (-0.2, 0.4)	0.448
TTD>2	24 (2.2%)	0.5 (-0.2, 1.2)	0.126
Subtype			
Classic	1019 (92.1%)	0	
Other types	87 (7.9%)	-0.5 (-0.8, -0.1)	0.013
ETE			
Absent	816 (73.8%)	0	
Present	290 (26.2%)	0.4 (0.1, 0.6)	0.002
Infiltration			
Present	1067 (96.5%)	0	
Absent	39 (3.5%)	0.9 (0.3, 1.4)	0.003
Multifocal			
Absent	717 (64.8%)	0	
Present	389 (35.2%)	-0.2 (-0.4, 0.1)	0.143
Hashimoto			
Absent	791 (71.5%)	0	
Present	315 (28.5%)	0.1 (-0.1, 0.3)	0.315
Age (years)			
<45	466 (42.1%)	0	
≥45	640 (57.9%)	-0.6 (-0.8, -0.4)	<0.001
Sex			
Female	922 (83.4%)	0	
Male	184 (16.6%)	0.4 (0.1, 0.6)	0.012

TTD: total tumor diameter, ETE: extrathyroid extension, LNM: lymph node metastasis.

Table 3. Effects of TTD on LNM number by stratified analysis

	N	Odds ratio (95% CI)	*p* value
Age (years)			
<45			
TTD≤0.5	185	0	
0.5<TTD≤1	207	0.1 (-0.3, 0.5)	0.6456
1<TTD≤2	64	-0.1 (-0.7, 0.5)	0.7529
TTD>2	10	0.2 (-1.2, 1.6)	0.8202
≥45			
TTD≤0.5	270	0	
0.5<TTD≤1	276	0.3 (0.1, 0.5)	0.0031
1<TTD≤2	80	0.3 (0.0, 0.6)	0.0435
TTD>2	14	0.9 (0.2, 1.6)	0.0077
Sex			
Female			
TTD≤0.5	382	0	
0.5<TTD≤1	406	0.3 (0.0, 0.5)	0.0276
1<TTD≤2	116	0.3 (0.0, 0.6)	0.0788
TTD>2	17	0.3 (-0.4, 1.1)	0.4072
Male			
TTD≤0.5	72	0	
0.5<TTD≤1	77	0.2 (-0.6, 0.9)	0.6697
1<TTD≤2	28	-0.5 (-1.5, 0.5)	0.3122
TTD>2	7	1.0 (-0.7, 2.8)	0.2502
BMI Tertile			
Low			
TTD≤0.5	142	0	
0.5<TTD≤1	166	0.1 (-0.4, 0.5)	0.8065
1<TTD≤2	52	0.0 (-0.6, 0.6)	0.9832
TTD>2	5	-0.6 (-2.4, 1.2)	0.5202
Middle			
TTD≤0.5	164	0	
0.5<TTD≤1	156	0.4 (0.1, 0.7)	0.0089
1<TTD≤2	44	0.3 (-0.2, 0.7)	0.2367
TTD>2	7	1.4 (0.4, 2.4)	0.0065
High			
TTD≤0.5	148	0	
0.5<TTD≤1	161	0.2 (-0.2, 0.6)	0.2842
1<TTD≤2	48	0.1 (-0.4, 0.7)	0.6304
TTD>2	12	0.6 (-0.5, 1.6)	0.2816

TTD: total tumor diameter, ETE: extrathyroid extension, LNM: lymph node metastasis.

founders (**Figure 2**). All data were double entered and then exported to tab-delimited text files. All *P* values were 2-sided and P less than 0.05 was considered significant. All analyses were performed with R (http://www.R-project.org) and EmpowerStats software (www.empowerstats.com, X&Y solutions, Inc. Boston MA).

Results

Patient information

Among the 1106 patients included in the study, there were 455 (41.1%), 483 (43.7%), 144 (13.0%) and 24 (2.2%) with the TTD≤0.5 cm, 0.5<TTD≤1 cm, 1<TTD≤2 cm and TTD>2 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 to be significantly different in regard of different TTD diameter (P=0.0017). In addition, associa-

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

	Non-adjusted OR (95% CI) P	Adjust I OR (95% CI) P	Adjust II OR (95% CI) P
TTD			
TTD≤0.5	0	0	0
0.5<TTD≤1	0.2 (0.0, 0.5) 0.0351	0.2 (0.0, 0.4) 0.0451	0.2 (0.0, 0.4) 0.0417
1<TTD≤2	0.2 (-0.2, 0.5) 0.3332	0.1 (-0.2, 0.4) 0.4477	0.1 (-0.2, 0.4) 0.4434
TTD>2	0.6 (-0.1, 1.3) 0.0991	0.5 (-0.2, 1.2) 0.1256	0.5 (-0.2, 1.2) 0.1441
Subtype			
Classic	0	0	0
Other types	-0.5 (-0.9, -0.2) 0.0049	-0.5 (-0.8, -0.1) 0.0133	-0.5 (-0.9, -0.1) 0.0112
ETE			
Absent	0	0	0
Present	0.4 (0.1, 0.6) 0.0018	0.4 (0.1, 0.6) 0.0023	0.4 (0.1, 0.6) 0.002
Infiltration			
Absent	0	0	0
Present	0.9 (0.3, 1.4) 0.0022	0.8 (0.3, 1.4) 0.0027	0.8 (0.3, 1.4) 0.0029
Multifocal			
Absent	0	0	0
Present	-0.1 (-0.3, 0.1) 0.2588	-0.2 (-0.4, 0.1) 0.1427	-0.2 (-0.4, 0.0) 0.1237
Hashimoto			
Absent			
Present	0.1 (-0.1, 0.3) 0.3502	0.1 (-0.1, 0.3) 0.3149	0.1 (-0.1, 0.3) 0.3078

TTD: total 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).

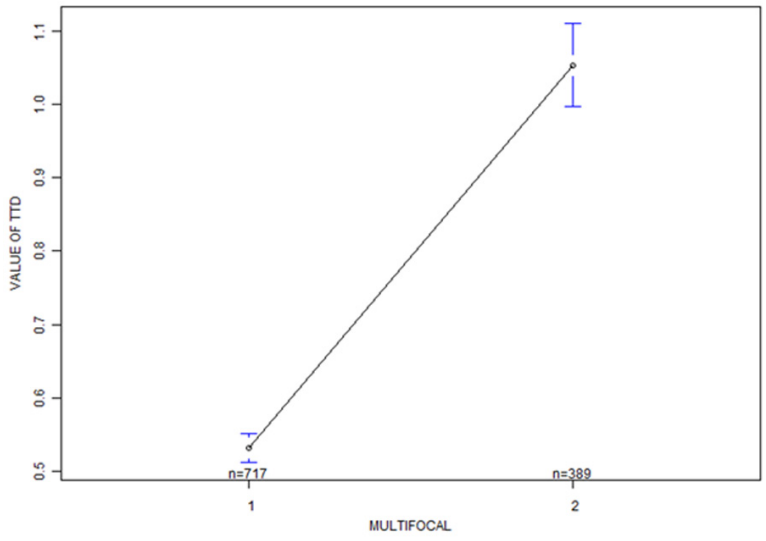

Figure 1. Correlation between value of TTD and multifocality by two-way ANOVA analysis. There was an obvious interaction between value of TTD and multifocality (P<0.001).

tion between multifocality with TTD was also significant (P<0.01). Apart from these two factors, there was no noticeable difference between the basic characteristics of the four groups.

Univariate and multivariable analysis

Univariate regression analysis showed that TTD was significantly correlated with the number of metastatic lymph nodes in 0.5<TTD≤1 cm group (odds ratio [OR] 0.2, 95% confidence interval [CI]: 0.0-0.4, P=0.045). In addition, subtype (OR -0.5, 95% CI -0.8 - -0.1, P=0.013), ETE (OR 0.4, 95% CI 0.1-0.6, P=0.002), infiltration (OR 0.9, 95% CI 0.3-1.4, P=0.003), age (OR -0.6, 95% CI -0.8 - -0.4, P<0.001), sex (OR 0.4, 95% CI 0.1-0.6, P= 0.012) also associated with the number of metastatic lymph nodes (**Table 2**). The stratified analysis suggested that TTD had a positive correlation with the number of metastatic lymph nodes in patients ≥45 years old. In addition, 0.5<TTD≤1 had a positive correlation with the number of metastatic lymph nodes in female patients compared to

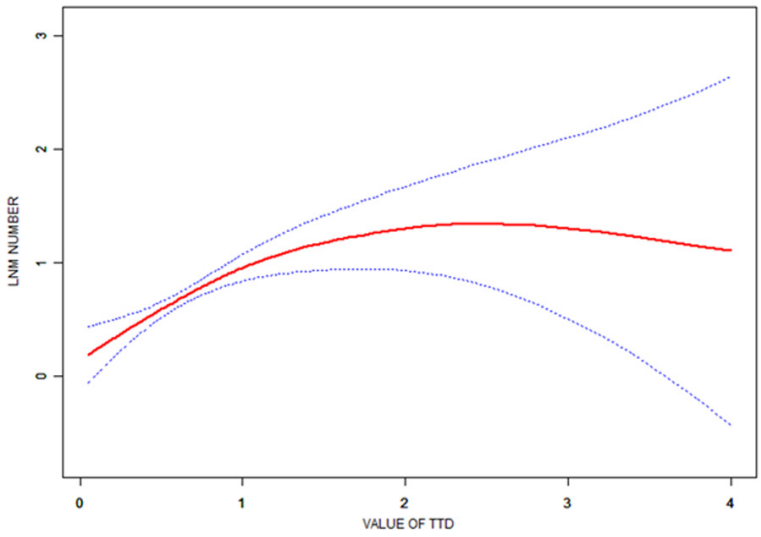

Figure 2. The relationship between the value of TTD and metastatic number of lymph nodes. A linear relationship between the value of TTD and metastatic number of lymph nodes was observed after adjusting for age, sex, BMI, extrathyroid extension, infiltration, multifocility, and combined Hashimoto.

Table 5. Threshold effect analysis of TTD on metastatic number of lymph nodes using piecewiselinear regression

Outcome	β (95% CI)	*P* value
Turning point (K): 1		
<K	1.0 (0.6, 1.4)	<0.001
>K	0.1 (-0.3, 0.5)	0.729

TTD: total tumor diameter.

TTD≤0.5. What's more, in the middle BMI group, 0.5<TTD≤1, TTD>2 had a positive correlation with the number of metastatic lymph nodes compared to TTD≤0.5 (**Table 3**). After multivariable risk adjustment for potential confounding factors (**Table 4**), 0.5<TTD≤1, Subtype, ETE and infiltration were found to be independently and positively associated with the number of metastatic lymph nodes.

Curve fitting analysis

Finally, we found that TTD was obviously correlated with the multifocality (P<0.001) using two-way ANOVA analysis (**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 TTD and the number of metastatic lymph nodes was observed (**Figure 2**). The number of LNMs increased with increasing TTD level when below the turning point (TTD<1 cm) (OR 1.0, 95% CI 0.6-1.4; P<0.001) (**Table 5**).

Discussion

PTMC is being diagnosed with increasing frequency worldwide and nearly constitutes nearly one-half all cases of PTC [11-13]. PTMC enjoys an excellent prognosis, however, 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 or PTMC recurrence in these susceptible patients [14-16].

According to The American Joint Committee on Cancer TNM classification, the concept of the number of metastatic lymph nodes was also mentioned as an important factor for clinicians when deciding on the need for completion thyroidectomy, further complete central lymph node dissection, or postoperative radioactive iodine treatment [17]. Investigating the risk factors for the number of metastatic lymph nodes may help predict the risk of LNM, with high clinical significance [17, 18].

Persistent disease and recurrence demand aggressive therapy and can affect the PTC patients' quality of life [4, 19, 20]. For example, recurrence increases the risk of reoperations and the exposure to a high cumulative radioiodine dose. And it has been recently reported that the number of metastatic lymph nodes may also be a statistical significant predictive factor associated with disease recurrence [9, 10]. Adam et al. provided information regarding the impact of the number of metastatic cervical lymph nodes on survival and demonstrated that an increasing number of metastatic lymph nodes (≤6) was associated with decreasing overall survival, therefore, they suggested that for patients with six or fewer metastatic lymph nodes, rigorous preoperative screening for additional nodal metastases in PTC should be advocated [9]. Lee et al. also showed the num-

ber of metastatic lymph nodes in risk stratification for recurrence in PTC and found that the number of metastatic lymph nodes was a significant prognostic factor. In addition, patients with ≥2 metastatic lymph nodes may benefit from radical treatment such as total thyroidectomy and radioactive iodine therapy [10].

Wang et al. have investigated the prognostic utility of a 1-cm cutoff as a predictor of outcome in DTC using a large, single-institutional database of thyroid cancer patients, and found that a distinction between tumors of <1 and >1 cm is of no prognostic benefit [21]. Therefore, the tumor size standard of AJCC still needs to be improved. Furthermore, scholars have suggested that TTD was a more accurate diameter than maximum tumor diameter as measure standard for tumor size in PTMC [1, 22]. Buffet et al. showed that for PMC Nx patients, total foci size of multifocal tumors more than 20 mm was significantly associated with recurrence [22]. Zhao et al. demonstrated that TTD more than 1 cm has a similar risk of LNM as a clinical papillary cancer [1].

In our results, we demonstrated that TTD, Subtype, ETE and infiltration were positively associated with LNM number after multivariable risk adjustment for potential confounding factors in PTMC. Moreover, to minimize the confounding effects of the primary tumor and to exclusively focus on the TTD effect on the number of metastatic lymph nodes, its linear relationship with the TTD was taken into consideration, and, after adjusting for this and other possible confounding factors, it was found that the number of metastatic lymph nodes significantly increased with the increasing TTD. Therefore, further treatment for the lateral neck should be considered in patients with larger TTD.

In our study, not all lymph node dissections were complete lateral neck dissections; therefore, the rate of lymph node metastasis may be underrepresented due to the incomplete histologic evaluation of regional lymph nodes in all patients. Additionally, other limitation in our study is the relatively small number of PTMC patients with lymph nodes metastasis (283 of total 1106). In addition, the data analyzed in this study were retrieved only from a single institution, which might result in selection bias and thereby weakening the statistical power.

Conclusion

In conclusion, our findings suggest that TTD is associated with the number of metastatic lymph node in PTMC. Thus, larger TTD patients may benefit from radical treatment such as total thyroidectomy and radioactive iodine therapy in PTMC.

Disclosure of conflict of interest

None.

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