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Original Article

Effects of age range on the number of metastatic lymph nodes in papillary thyroid microcarcinoma

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Abstract: *Purpose:* Whether clinicopathologic risk factors are associated with the number of metastatic lymph nodes remains unclear. Thus, this study aimed to investigate the effects of age range on the number of metastatic lymph nodes in papillary thyroid microcarcinoma (PTMC). *Methods:* A series of 1115 patients with PTMC who underwent total thyroidectomy plus central lymph node dissection were analyzed. The clinical correlation between the number of metastatic lymph nodes and age range was retrospectively studied after adjusting for potential confounders. *Results:* Lymph node metastases were found more frequently in the age <45 group than in the age ≥45 group (P<0.001). Univariate regression analysis showed that age was significantly correlated with the number of metastatic lymph nodes (odds ratio -0.6, 95% confidence interval -0.8 to -0.4, P<0.001). After multivariable risk adjustment for potential confounding factors, age, subtype, extrathyroid extension, infiltration, and maximum tumor size remained positively associated with the number of metastatic lymph nodes. A linear relationship between age and the number of metastatic lymph nodes was observed: when below the turning point (56 years), the number of metastatic lymph nodes decreasing with the increasing age. *Conclusions:* Our findings suggest that age is associated with the number of metastatic lymph nodes in PTMC. Radical treatment may be necessary for younger PTMC patients.

Keywords: Papillary thyroid microcarcinoma, lymph node metastasis, age

Introduction

Papillary thyroid microcarcinoma (PTMC) is defined as papillary thyroid carcinoma (PTC) measuring ≤1.0 cm in its greatest dimension according to the World Health Organization classification system [1-3]. PTMCs are diagnosed with increasing frequency, owing to the increased accuracy of pathologic thyroid examinations, in particular due to the increasing thinness and number of the anatomical slices obtained from thyroid specimens [4, 5]. Thus, the increased incidence of thyroid cancer can partly be accounted for by the increased incidence of PTMC [6].

The number of metastatic lymph nodes and the ratio between the number of metastatic lymph nodes and harvested lymph nodes have been demonstrated to be predictors of prognosis in PTMC [7]; however, better knowledge about the predictors of the number of metastatic lymph nodes in PTMC is required.

Risk factors for lymph node metastasis (LNM), especially central LNM, have been reported to include age <45 years, extrathyroid extension (ETE), multifocal disease, and maximum tumor size (MTD) >0.5 cm, among others [2, 3, 8, 9]. However, whether these risk factors are also associated with the number of metastatic lymph nodes remains unclear. Thus, in this study, we aimed to investigate the effects of age distribution on the number of metastatic lymph nodes in PTMC.

Materials and methods

Study population

A total of 1115 consecutive patients with PTMC who underwent total-thyroidectomy plus cen-

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

Characteristics	Age <45	Age ≥45	*P*-value
Sex			0.616
Female	386 (82.5%)	541 (83.6%)	
Male	82 (17.5%)	106 (16.4%)	
LNM			<0.001
Absent	302 (64.5%)	530 (81.9%)	
Present	166 (35.5%)	117 (18.1%)	
Subtype			0.118
Classic	438 (93.6%)	589 (91.0%)	
Other types	30 (6.4%)	58 (9.0%)	
ETE			0.594
Absent	342 (73.1%)	482 (74.5%)	
Present	126 (26.9%)	165 (25.5%)	
Infiltration			0.590
Absent	450 (96.2%)	626 (96.8%)	
Present	18 (3.8%)	21 (3.2%)	
Multifocal			0.353
Absent	297 (63.5%)	428 (66.2%)	
Present	171 (36.5%)	219 (33.8%)	
Hashimoto			0.870
Absent	337 (72.0%)	463 (71.6%)	
Present	131 (28.0%)	184 (28.4%)	
MTD			0.821
≤0.5	242 (51.7%)	339 (52.4%)	
0.5<MTD≤1	226 (48.3%)	308 (47.6%)	

MTD: Maximum tumor size, ETE: Extrathyroid extension, LNM: Lymph node metastasis.

tral lymph node dissection at union hospital between January 2003 and January 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.

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 in the patients undergoing lobectomy and in the patients being 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. MTD was defined to be the largest diameter of dominant tumor of PTMCs.

Statistical analysis

We first compared the data distribution of each covariate between the exposed and the non-exposed groups, using the t test (normal distribution) or Kruskal-Wallis rank sumtest (non-normal distribution) for continuous variables and Chi-square tests for categorical data (**Table 1**). Next, univariate logistic regression (**Table 2**) and multivariate logistic regression models (**Table 3**) were used to examine whether age distribution and other covariates had an independent effect on metastasis number of lymph node separately. The two-way ANOVA analysis was used to analyze the distribution of metastasis number of lymph node and age in PTMCs. Then we explored the relationship between age distribution and metastasis number of lymph node by the smoothing plot, with an adjustment for potential confounders (**Figure 2**). All data were double entered and then exported to tab-delimited text files. All analyses were performed with R (http://www.R-project.org) and EmpowerStats software (www.empowerstats.com, X&Y solutions, Inc.Boston MA).

Results

Among the 1115 patients included in the study, there were 468 (42.0%) and 647 (58.0%) patients aged <45 and ≥45 years, respectively (**Figure 1**). The demographic and clinical characteristics of the analyzed patients, including, sex, LNM, subtype, ETE, infiltration, multifocal, concomitant presence of Hashimoto's disease, and MTD, are summarized in **Table 1**. Of note, LNMs were found more frequently in patients aged <45 than in those aged ≥45 (P<0.001). However, apart from the number of metastatic lymph nodes, there was no noticeable difference in the basic characteristics between the two age groups.

Univariate regression analysis showed that age was significantly correlated with the number of

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

	Statistics	Odds ratio (95% CI)	*p* value
Age (years)			
<45	468 (42.0%)	0	
≥45	647 (58.0%)	-0.6 (-0.8, -0.4)	<0.001
Sex			
Female	928 (83.2%)	0	
Male	187 (16.8%)	0.3 (0.1, 0.6)	0.014
MTD (cm)			
≤0.5	581 (52.1%)	0	
0.5<MTD≤1	534 (47.9%)	0.2 (0.0, 0.4)	0.017
Subtype			
Classic	1027 (92.1%)	0	
Other types	88 (7.9%)	-0.5 (-0.9, -0.2)	0.005
ETE			
Absent	824 (73.9%)	0	
Present	291 (26.1%)	0.4 (0.1, 0.6)	0.002
Infiltration			
Absent	1076 (96.5%)	0	
Present	39 (3.5%)	0.9 (0.3, 1.4)	0.002
Multifocal			
Absent	725 (65.0%)	0	
Present	390 (35.0%)	-0.1 (-0.3, 0.1)	0.283
Hashimoto			
Absent	800 (71.7%)	0	
Present	315 (28.3%)	0.1 (-0.1, 0.3)	0.315

MTD: Maximum tumor size, ETE: Extrathyroid extension, LNM: Lymph node metastasis.

metastatic lymph nodes (odds ratio [OR] -0.6, 95% confidence interval [CI] -0.8 to -0.4, P< 0.001). In addition, sex (OR 0.3, 95% CI 0.1-0.6, P = 0.014), subtype (OR -0.5, 95% CI -0.9 to -0.2, P = 0.005), MTD (OR 0.2, 95% CI 0.0-0.4, P = 0.017), ETE (OR 0.4, 95% CI 0.1-0.6, P = 0.002), and infiltration (OR 0.9, 95% CI 0.3-1.4, P = 0.002) also associated with the number of metastatic lymph nodes. Conversely, no association was seen with multifocality or combined Hashimoto's disease (**Table 2**). After multivariable risk adjustment for potential confounding factors (**Table 3**), age, subtype, ETE, infiltration, and MTD were found to be independently and positively associated with the number of metastatic lymph nodes.

Finally, we found that there was an obvious interaction between the age value and number of metastatic lymph nodes (P<0.001) using two-way ANOVA analysis (**Figure 2**). After adjusting for the possible factors related to the number of metastatic lymph nodes, including sex, body mass index, ETE, infiltration, multifocality, MTD, and combined Hashimoto, a linear relationship between age and the number of metastatic lymph nodes was observed when below the turning point (56 years) (**Figure 3**; **Table 4**), with the number of metastatic lymph nodes significantly decreasing along with age in these patients (OR 0.0, 95% CI -0.1 to 0.0, P<0.001).

Discussion

PTMC is an indolent disease, but is associated with a risk of LNM and local recurrence [9]. Moreover, LNM at the time of initial operation significantly relates to postoperative recurrence, and the follow-up evaluations must be enhanced after the initial treatment to mitigate PTC or PTMC recurrence in these patients [2, 10, 11].

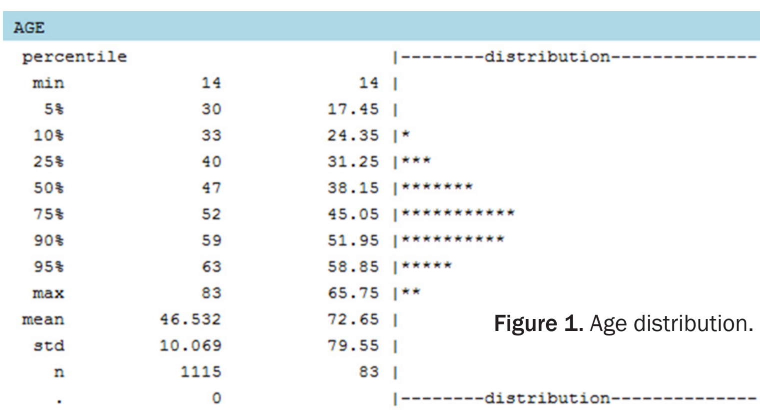
Further, it has been recently reported that the number of metastatic lymph nodes may be a statistical significant predictive factor associated with disease recurrence [11-14]. Lee et al. investigated the significance of the number of metastatic lymph nodes in risk stratification for recurrence in PTC and found that the number of metastatic lymph nodes was a significant prognostic factor, concluding that it should be considered as part of the postoperative staging system as a means to tailor the treatment and follow-up recommendations for each individual patient. In addition, patients with ≥2 metastatic lymph nodes may benefit from radical treatments such as total thyroidectomy and radioactive iodine therapy [13]. Adam et al. also reported that an increasing number of metastatic lymph nodes (≤6) was associated with decreasing overall survival, and therefore suggested that, for patients with six or fewer metastatic lymph nodes, rigorous preoperative screening for additional nodal metastases in PTC should be advocated [12].

The American Joint Committee on Cancer TNM classification is currently being used in most clinical practices. Regarding the N staging system, the 7th edition classifies LNMs into simple binary categories (presence vs. absence) based

Table 3. Multivariate logistic regression model for risk factors associated with LNM number

Exposure	Non-adjusted	Adjust
AGE		
<45	0	0
≥45	-0.6 (-0.8, -0.4) <0.001	-0.6 (-0.8, -0.4) <0.001
Subtype		
Classic	0	0
Other types	-0.5 (-0.9, -0.2) 0.005	-0.5 (-0.9, -0.2) 0.006
ETE		
Absent	0	0
Present	0.4 (0.1, 0.6) 0.002	0.4 (0.1, 0.6) 0.002
Infiltration		
Absent	0	0
Present	0.9 (0.3, 1.4) 0.002	0.9 (0.3, 1.4) 0.002
Multifocal		
Absent	0	0
Present	-0.1 (-0.3, 0.1) 0.283	-0.1 (-0.3, 0.1) 0.221
Hashimoto		
Absent	0	0
Present	0.1 (-0.1, 0.3) 0.315	0.1 (-0.1, 0.3) 0.301
MTD12		
≤0.5	0	0
0.5<MTD≤1	0.2 (0.0, 0.4) 0.017	0.2 (0.0, 0.4) 0.022

MTD: Maximum tumor size, ETE: Extrathyroid extension, LNM: Lymph node metastasis. Odds ratios were derived from multivariate logistic regression analysis. Adjust model adjust for: SEX; BMI.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AGE
 percentile                          |--------distribution--------------
  min          14            14  |
   5%          30         17.45  |
  10%          33         24.35  |*
  25%          40         31.25  |***
  50%          47         38.15  |*******
  75%          52         45.05  |***********
  90%          59         51.95  |**********
  95%          63         58.85  |*****
  max          83         65.75  |**
 mean      46.532         72.65  |
  std      10.069         79.55  |
    n        1115            83  |
    .           0                |--------distribution--------------
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Figure 1. Age distribution.

on the anatomic location. In the latest American Joint Committee on Cancer staging system, however, 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 [15]. Therefore, investigating the risk factors for the number of metastatic lymph nodes may help predict the risk of LNM, with high clinical significance [7].

Some groups have studied the clinical and pathologic features predictive of lymph node metastasis, which may help guide treatment decisions. However, the conclusions of these studies have varied, and further investigation is warranted [9, 16-18]. One important clinical feature is the age distribution of the patients [19]. Guo et al. illustrated that age <45 years was associated with and was an independent prognostic factor of central LNM in PTMC [3]. However, age did not correlate with an increased risk of LNM in Lee et al.'s study. Hence, the present study further analyzed the relationship between age distribution with LNM and number of metastatic lymph nodes in PTMC.

In our results, we demonstrated that age, MTD, subtype, ETE, and infiltration were positively associated with the number of metastatic lymph nodes 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 age effect on the number of metastatic lymph nodes, its linear relationship with the MTD 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 decreased with increasing age, up until age 56. Therefore, further treatment for the lateral neck should be considered in younger patients, especially in those aged less than 45 years.

There are some limitations to our study. First, the relatively small number of PTMC patients

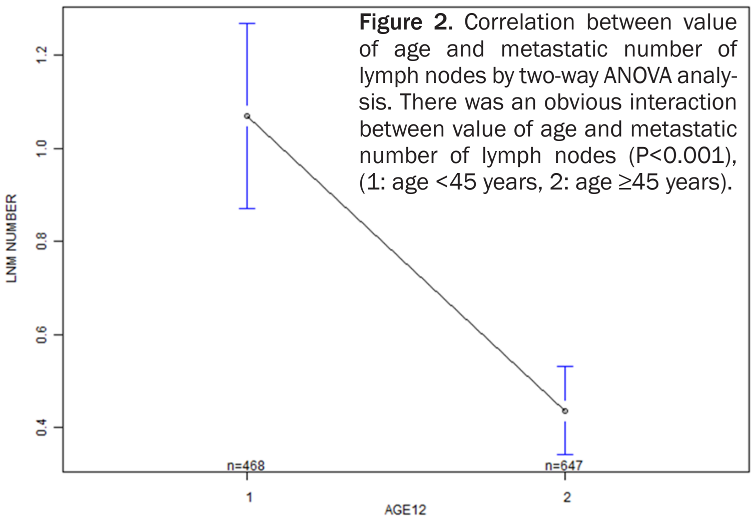

Figure 2. Correlation between value of age and metastatic number of lymph nodes by two-way ANOVA analysis. There was an obvious interaction between value of age and metastatic number of lymph nodes (P<0.001), (1: age <45 years, 2: age ≥45 years).

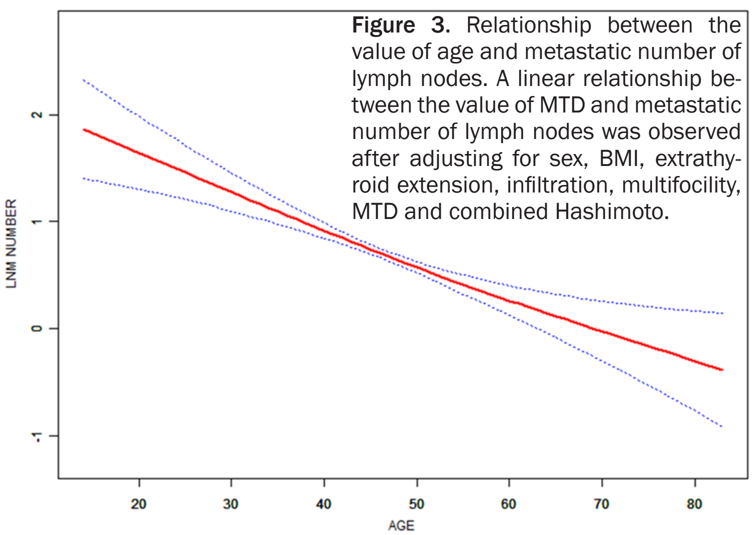

Figure 3. Relationship between the value of age and metastatic number of lymph nodes. A linear relationship between the value of MTD and metastatic number of lymph nodes was observed after adjusting for sex, BMI, extrathyroid extension, infiltration, multifocility, MTD and combined Hashimoto.

Table 4. Threshold effect analysis of age distribution on metastatic number of lymph nodes using piecewise linear regression

Outcome	β (95% CI)	*P* value
Turning point (K): 56		
<K	0.0 (-0.1, 0.0)	<0.001
>K	0.0 (0.0, 0.0)	0.823

with lymph nodes metastasis (283 of the total 1115 patients). Additionally, not all lymph node dissections were complete lateral neck dissections; therefore, the rate of lymph node metastasis may be underrepresented due to the incomplete histological evaluation of regional lymph nodes in all patients. 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.

In conclusion, our findings suggest that age is associated with the number of metastatic lymph node in PTMC. Thus, taking the age of the patients into consideration may help direct the treatment decisions for PTMC.

Disclosure of conflict of interest

None.

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