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Original Article

The effects of maximum tumor diameter on metastasic number of lymph node in papillary thyroid microcarcinoma

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Abstract: Objective: Whether clinicopathologic risk factors such as Maximum tumor diameter (MTD) 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 MTD 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 MTD was retrospectively studied after adjusting for potential confounders. Univariate and multivariate logistic regression models were used to assess whether MTD and other covariates had independent effects on the number of metastatic lymph nodes. The relationship between MTD and the number of metastatic lymph nodes was subsequently explored using a smoothing plot. Results: LNM were found more frequently in the 0.5<MTD≤1 cm group than in those ≤0.5 cm group (P<0.001). Univariate regression analysis showed that MTD was significantly correlated with the number of metastatic lymph nodes (odds ratio 0.2, 95% confidence interval: 0.0-0.4, P=0.019). After multivariable risk adjustment for potential confounding factors, MTD, Subtype, extrathyroid extension and infiltration remained positively associated with the number of metastatic lymph nodes. A linear relationship between MTD and metastasic number of lymph node was observed. In these patients, the number of LNMs increased with increasing MTD level (OR 0.8, 95% CI 0.4, 1.2; P<0.001). Conclusions: Our findings suggest that MTD is associated with metastasic number of lymph node in PTMCs. Radical treatment may be necessary for larger MTD patients.

Keywords: Maximum tumor size, metastasic number of lymph node, papillary thyroid microcarcinoma

Introduction

Papillary thyroid carcinoma (PTC) is the most common malignant thyroid neoplasm, accounting for 80% of all thyroid cancers [1]. 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 [2-4]. PTMCs are diagnosed with increasing frequency, 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, 5, 6]. The incidence increase of thyroid cancer can partly be accounted for by the increased incidence of PTMC [7].

The number of metastatic lymph node, 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]; however, better knowledge about the predictors for number of metastatic lymph node in PTMC is required.

Clinicopathological risk factors for lymph node metastasis (LNM) especially central lymph node metastasis (CLNM) in PTMC have been reported by many recent studies to include extrathyroid extension (ETE), multifocal dis-

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

Characteristics	MTD≤0.5 cm	0.5<MTD≤1 cm	*P*-value
Age (years)			0.877
<45	241 (51.72%)	225 (48.28%)	
≥45	334 (52.19%)	306 (47.81%)	
Sex			0.459
Female	483 (52.44%)	438 (47.56%)	
Male	92 (49.46%)	93 (50.54%)	
LNM			<0.001
Absent	460 (55.89%)	363 (44.11%)	
Present	115 (40.64%)	168 (59.36%)	
Subtype			0.618
Classic	532 (52.21%)	487 (47.79%)	
Other types	43 (49.43%)	44 (50.57%)	
ETE			0.430
Absent	430 (52.7%)	386 (47.3%)	
Present	145 (50.00%)	145 (50.00%)	
Infiltration			0.677
Absent	556 (52.11%)	511 (47.89%)	
Present	19 (48.72%)	20 (51.28%)	
Multifocal			0.011
Absent	393 (54.81%)	324 (45.19%)	
Present	182 (46.79%)	207 (53.21%)	
Hashimoto			0.335
Absent	404 (51.07%)	387 (48.93%)	
Present	171 (54.29%)	144 (45.71%)	

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

ease, maximum tumor diameter (MTD) >0.5 cm, less than 45 years, among others [3, 4, 9-11]. However, whether these risk factors are associated with number of metastatic lymph node remains unclear. Thus, in this study, we aimed to investigate the effects of value of MTD on number of metastasic lymph node in PTMC.

Materials and methods

Study population

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 PTMC, regardless of size, foci number and disease stage. When preoperative imaging test such as ultrasound indicated suspicious lymph node metastasis in lateral neck, we would choose lateral neck dissection. Fine-needle aspiration biopsy (FNAB) and/or intraoperative frozen section examination is routinely performed during a thyroid surgical procedure. Forty-four 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 and 32 false-positive cases were excluded from analysis. 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 in department of pathology of Union hospital. 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 less MTD (≤0.5 cm) and the larger MTD groups (0.5<MTD≤1 cm), 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 MTD and other covariates had an independent effect on metastastic number of lymph node separately. The two-way ANOVA analysis was used to analyze the distribution of metastasic number of lymph node and MTD in PTMCs. Then we explored the relationship between MTD and metastasic 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

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

	Statistics	Odds ratio (95% CI)
MTD (cm)		
≤0.5	575 (52.0%)	0
0.5<MTD≤1	531 (48.0%)	0.2 (0.0, 0.4)
Subtype		
Classic	1019 (92.1%)	0
Other types	87 (7.9%)	-0.5 (-0.9, -0.2)
ETE		
Absent	816 (73.8%)	0
Present	290 (26.2%)	0.4 (0.1, 0.6)
Absent		
Infiltration		
Present	1067 (96.5%)	0
Absent	39 (3.5%)	0.9 (0.3, 1.4)
Multifocal		
Absent	717 (64.8%)	0
Present	389 (35.2%)	-0.1 (-0.3, 0.1)
Hashimoto		
Absent	791 (71.5%)	0
Present	315 (28.5%)	0.1 (-0.1, 0.3)
Age (years)		
<45	466 (42.1%)	0
≥45	640 (57.9%)	-0.6 (-0.8, -0.4)
Sex		
Female	921 (83.3%)	0
Male	184 (16.7%)	0.4 (0.1, 0.6)

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

(http://www.R-project.org) and EmpowerStats software (www.empowerstats.com, X&Y solutions, Inc. Boston MA).

Results

Among the 1106 patients included in the study, 73 cases were performed lateral neck dissection and there were 575 (52.0%) and 531 (48.0%) with the MTD≤0.5 cm and 0.5<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 0.5<MTD≤1 cm group than in the MTD≤0.5 cm group (P<0.001). In addition, multifocality was more common in the 0.5<MTD≤1 cm group (P=0.011). Apart from these two factors, there was no noticeable difference between the basic characteristics of the two groups.

Univariate regression analysis showed that MTD was significantly correlated with the number of metastatic lymph nodes (odds ratio [OR] 0.2, 95% confidence interval [CI]: 0.0-0.4, P=0.019). In addition, subtype (OR-0.5, 95% CI -0.9-0.2, P=0.019), ETE (OR 0.4, 95% CI 0.1-0.6, P=0.002), infiltration (OR 0.9, 95% CI 0.3-1.4, P=0.002), 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 MTD had a positive correlation with the number of metastatic lymph nodes in patients who ≥45 years old, women, and the middle BMI group. Subtype was associated with the number of metastatic lymph nodes in patients <45 years old, women, and the middle BMI group. ETE was associated with the number of metastatic lymph nodes in patients <45 years old and the low BMI group, regardless of sex. Infiltration was associated with the number of metastatic lymph nodes in women and the middle BMI group, regardless of age (**Table 3**). After multivariable risk adjustment for potential confounding factors (**Table 4**), MTD, Subtype, ETE and infiltration 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 MTD level in these patients (OR 0.8, 95% CI 0.4, 1.2; P<0.001).

Discussion

Roughly 50% of PTC increase is attributable to the identification of intrathyroidal papillary thyroid microcarcinomas [12]. Although PTMC is an indolent disease, it does pose a risk for lymph node metastasis and local recurrence [10]. Moreover, LNM at the time of initial opera-

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

	N	Odds ratio (95% CI)	*P* value
MTD			
Age(years)			
<45	466	0.2 (-0.2, 0.6)	0.4078
≥45	640	0.3 (0.1, 0.5)	0.0024
Sex			
Female	921	0.3 (0.1, 0.5)	0.0111
Male	185	0.1 (-0.6, 0.7)	0.7942
BMI Tertile			
Low	365	0.1 (-0.3, 0.5)	0.7594
Middle	371	0.4 (0.1, 0.7)	0.0032
High	369	0.2 (-0.1, 0.6)	0.2353
Subtype			
Age (years)			
<45	466	-0.8 (-1.6, 0.0)	0.0528
≥45	640	-0.3 (-0.6, 0.0)	0.0642
Sex			
Female	921	-0.5 (-0.9, -0.1)	0.0102
Male	185	-0.8 (-2.1, 0.6)	0.2705
BMI Tertile			
Low	365	-0.4 (-1.1, 0.4)	0.3510
Middle	371	-0.5 (-1.0, -0.1)	0.0294
High	369	-0.7 (-1.5, 0.0)	0.0634
ETE			
Age (years)			
<45	466	0.6 (0.2, 1.0)	0.0089
≥45	640	0.2 (0.0, 0.4)	0.1102
Sex			
Female	921	0.3 (0.0, 0.5)	0.0193
Male	185	0.8 (0.0, 1.5)	0.0402
BMI Tertile			
Low	365	0.6 (0.2, 1.1)	0.0058
Middle	371	0.2 (-0.1, 0.5)	0.2924
High	369	0.3 (-0.2, 0.7)	0.2223
Infiltration			
Age (years)			
<45	466	1.1 (0.1, 2.1)	0.0402
≥45	640	0.6 (0.1, 1.2)	0.0216
Sex			
Female	921	0.8 (0.3, 1.4)	0.0032
Male	185	0.9 (-0.8, 2.6)	0.3058
BMI Tertile			
Low	365	0.7 (-0.3, 1.6)	0.1569
Middle	371	1.3 (0.5, 2.0)	0.0014
High	369	0.7 (-0.5, 1.8)	0.2771
Multifocal			
Age (years)			
<45	466	-0.3 (-0.7, 0.1)	0.1197
≥45	640	0.0 (-0.2, 0.2)	0.9970
Sex			
Female	921	-0.1 (-0.3, 0.1)	0.4715
Male	185	-0.4 (-1.1, 0.2)	0.2082
BMI Tertile			
Low	365	-0.3 (-0.7, 0.1)	0.1959
Middle	371	0.1 (-0.1, 0.4)	0.3318
High	369	-0.2 (-0.6, 0.1)	0.2248
Hashimoto			
Age (years)			
<45	466	0.2 (-0.3, 0.6)	0.4975
≥45	640	0.1 (-0.1, 0.3)	0.4390
Sex			
Female	921	0.2 (0.0, 0.4)	0.1019
Male	185	-0.3 (-1.0, 0.4)	0.4253
BMI Tertile			
Low	365	0.0 (-0.4, 0.5)	0.8982
Middle	371	-0.1 (-0.5, 0.2)	0.3722
High	369	0.4 (0.0, 0.8)	0.0714

tion 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 [12-14].

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. It has been recently reported that the number of metastatic lymph nodes may be a statistical significant predictive factor associated with disease recurrence [15-17]. 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 treatment such as total thyroidectomy and radioactive iodine therapy [16]. Adam et al. also reported that an increasing number of metastatic lymph nodes (≤6) was associated with decreasing overall survival, therefore, they suggested that for

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

	Non-adjusted	Adjust I	Adjust II
MTD	0.2 (0.0, 0.4) 0.0187	0.2 (0.0, 0.4) 0.0214	0.2 (0.0, 0.4) 0.0199
Subtype	-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	0.4 (0.1, 0.6) 0.0018	0.4 (0.1, 0.6) 0.0023	0.4 (0.1, 0.6) 0.0021
Infiltration	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	-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	0.1 (-0.1, 0.3) 0.3502	0.1 (-0.1, 0.3) 0.3149	0.1 (-0.1, 0.3) 0.3078

MTD: maximum tumor size, 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).

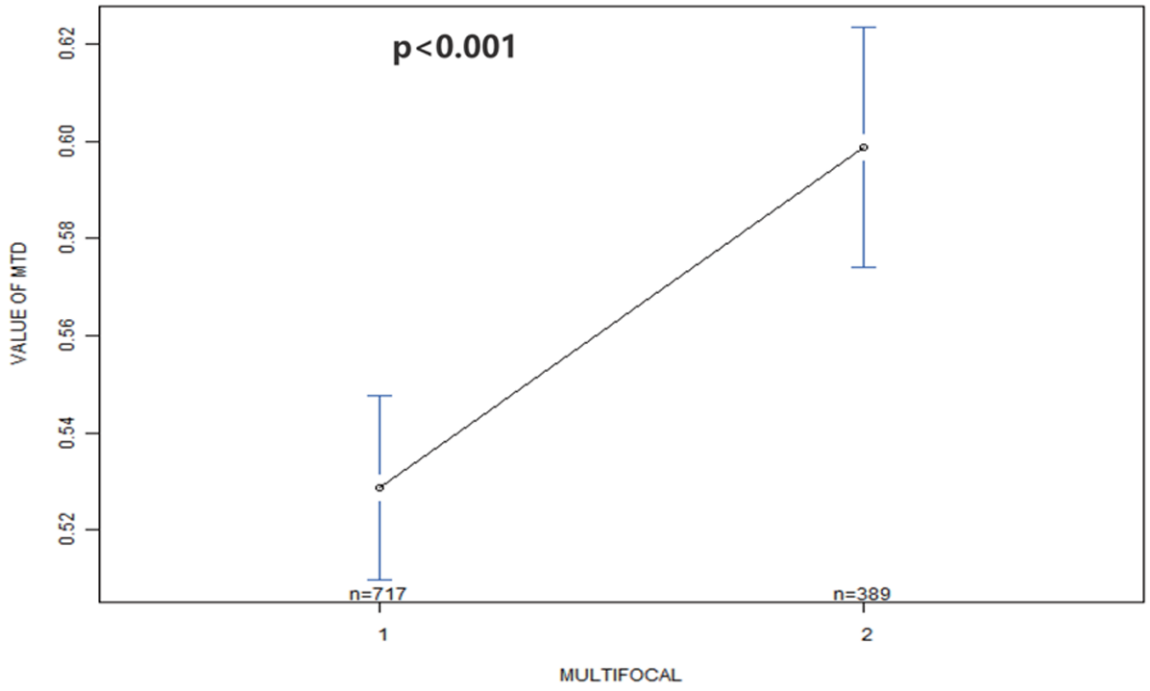

Figure 1. Correlation between value of MTD and multifocality by two-way ANOVA analysis. There was an obvious interaction between value of MTD and multifocality (P<0.001).

patients with six or fewer metastatic lymph nodes, rigorous preoperative screening for additional nodal metastases in PTC should be advocated [15].

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 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 [18]. Therefore, investigating the risk factors for the number of metastatic lymph nodes may help predict the risk of LNM, with high clinical significance [8].

Scholars 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 [10, 19-21]. One of the clinical features is the maximum tumor diameter (MTD) [22-25]. Our recent meta-analysis have illustrated that MTD≥0.5 cm was associated with

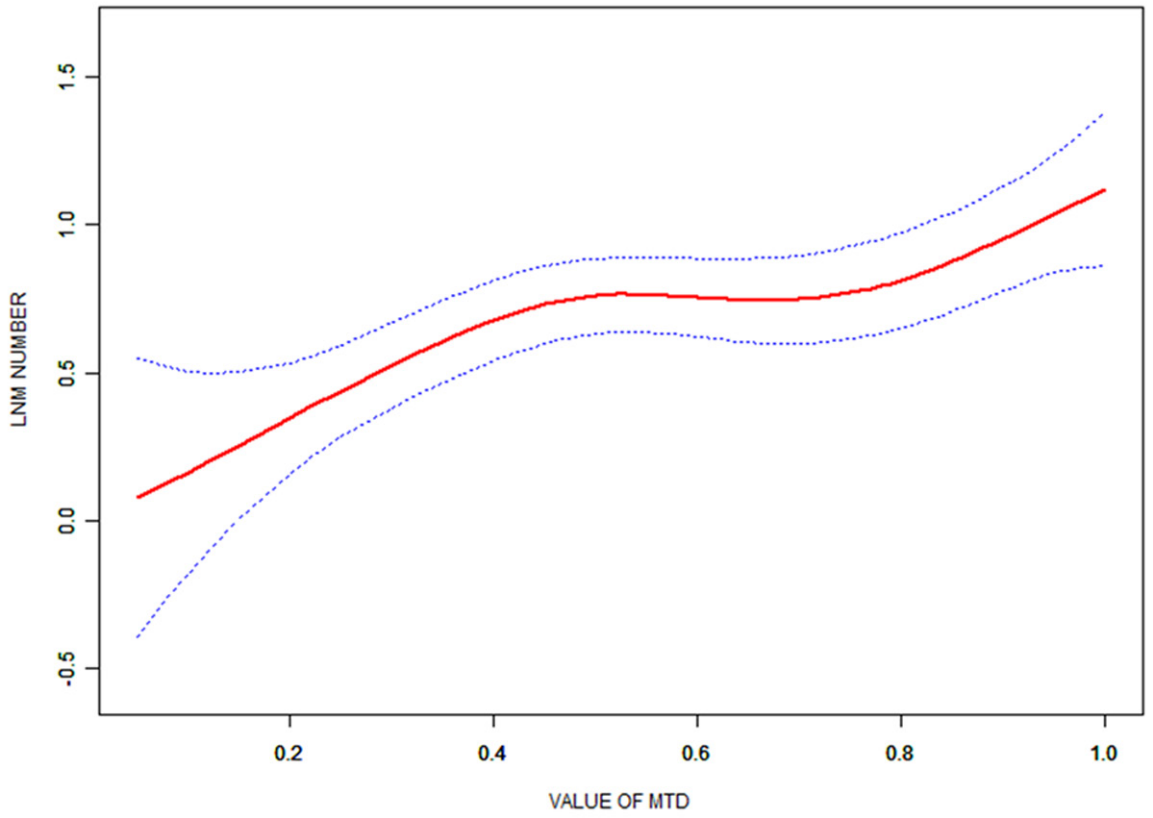

Figure 2. The relationship between the value of MTD and metastastic number of lymph nodes. A linear relationship between the value of MTD and metastastic number of lymph nodes was observed after adjusting for age, sex, BMI, extrathyroid extension, infiltration, multifocility, and combined Hashimoto.

central lymph node metastasis in PTMCs [4], However, tumor diameter was not correlated with an increased risk for CLNM in Siddiqui' study [10]. Further investigation was taken in this study to show the relationship between MTD with the number of metastatic lymph node in PTMCs.

Studies have showed that MTD greater than 3 cm is one of the risk factors for recurrence in the lymph node of papillary thyroid cancer [26-29]. In our results, we demonstrated that MTD, 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 MTD 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 increased with the increasing MTD. Therefore, further treatment for the lateral neck should be considered in patients with MTD more than 0.5 cm.

One of the limitations in our study is the relatively small number of PTMC patients with lymph nodes metastasis (283 of total 1106). 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 histologic 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.

Conclusion

In conclusion, our findings suggest that MTD is associated with the number of metastatic lymph node in PTMC. Thus, taking MTD into

consideration may help direct the treatment decisions for PTMC.

Disclosure of conflict of interest

None.

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