



## Original Research

## Risk factors of central lymph node metastasis in papillary thyroid carcinoma: A retrospective cohort study

Tong Tang\*, Jia Li, Lu Zheng, Lei Zhang, Jianing Shi

Department of Thyroid and Breast Surgery, The Second Hospital of Anhui Medical University, China



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## ABSTRACT

**Objective:** The aim of this study was to explore the risk factors that were associated with central lymph node metastases (CLNM) in papillary thyroid carcinoma (PTC) patients.

**Methods:** A total of 180 patients with PTC who underwent surgery in our hospital between January 2014 and December 2016 were identified retrospectively. The relationship between clinicopathological factors and CLNM were analyzed by univariate and multivariate logistic regression.

**Results:** The incidence of CLNM was 67.8% (122/180) in PTC patients. Univariate analysis showed that multifocality ( $p = 0.002$ ), HT ( $p < 0.001$ ) and LVI ( $p < 0.001$ ) were significant associated with CLNM. No significant associations were found between factors and CLNM, including age, gender, tumor size and ETE. Multivariate logistic regression analysis showed that multifocality ( $p = 0.011$ ), HT ( $p < 0.001$ ) and LVI ( $p < 0.001$ ) were independent predictors of CLNM in PTC patients.

**Conclusions:** Our study identified several independent risk factors predicting CLNM in PTC patients, such as multifocality, HT and LVI. The CLNM is very common in PTC patients, and routine prophylactic central neck dissection (PCND) may recommended in PTC patients with those risk factors of CLNM.

## 1. Introduction

The incidence of thyroid cancer (TC) has more increased rapidly in the last few years [1,2]. Papillary thyroid cancer (PTC) is the most common histological subtype of thyroid malignant, accounting for approximately 80% of all thyroid cancers. It is estimated that about 90.0 per 1000 and 6.8 per 1000 of the thyroid cancer incidence rate and mortality rate in China in 2015 year [3]. Most cases of PTC have an indolent course and excellent prognosis, the long-term recurrence rate has been reported as high as 12% [4]. Current knowledge suggested that central lymph node metastases (CLNM) is the most important factors to increase the risk of local recurrence and overall survival [5–7].

There is general consensus that central compartment neck dissection (CCND) is recommend for PTC patients with CLNM. However, it remains controversial whether to perform prophylactic central neck dissection (PCND) in clinically node-negative PTC patients (cN<sub>0</sub> PTC) [8]. Some researchers suggested routine central cervical lymph node dissection (CCLND) in order to prevent a low morbidity rate and a future recurrence associated with first operation [9–11], whereas others reveal that this procedure increases the incidence of complications and whether it can really improve the survival rate [12,13].

Ultrasonography (US) is the main diagnostic tool for deciding the TNM stage of PTC before surgery. However, the high diagnostic accuracy in detecting the lateral lymph node metastasis, but the accuracy of preoperative US detecting CLNM is limited [14,15]. Consequently, it is important to identify the risk factors associated with CLNM in PTC. The aim of our study was to analyze the association between clinical features and CLNM in PTC patients, and discuss the predictive value of these features.

## 2. Materials and methods

## 2.1. Patients and data collection

A total of 202 patients with PTC who underwent thyroid surgery (any type of thyroidectomy or lobectomy) at our hospital between 2014 and 2016 were retrospectively collected in this study. Patients were not first primary PTC or had other head and neck malignant were excluded, and 180 patients were finally included. This retrospective study was approved by our Institutional Review Board. We reviewed electronic medical record and surgical pathology reports of each patient to define initial clinical pathological features, including tumor size, multifocality, lymph node metastasis, Hashimoto's thyroiditis (HT), lymphovascular

\* Corresponding author.

E-mail address: [tt20164@sina.com](mailto:tt20164@sina.com) (T. Tang).

invasion (LVI), and extrathyroidal extension (ETE).

Tumor size was defined as the largest diameter measured by pre-operative ultrasound. Multifocality was defined as more than 1 foci of PTC in total (either in the same lobe or different lobes). The positive nodes, HT, LVI and ETE were identified by definitive histopathology.

The work has been reported in line with the STROCSS criteria [16].

## 2.2. Statistical analysis

The data were analyzed by SPSS 16.0 statistical software (SPSS Inc., Chicago, IL, USA). Data are expressed as the mean  $\pm$  standard deviation (SD). Difference between categorical was analyzed by Chi-squared ( $\chi^2$ ) test. Univariate logistic and binary logistic regression were performed to investigate the relationship between clinicopathologic features and CLNM. A  $p$  value  $< 0.05$  was considered statistically significant.

## 3. Results

A total of 180 PTC patients, and 147 (81.7%) of them were female in this study. The clinicopathologic characteristics of all patients are summarized in Table 1. The mean age was 44.7 years with a range of 14–81 years. Of all the patients, 150 (83.3%) had tumor  $\leq 10$  mm in diameter, and 102 (56.7%) had multifocal tumors. HT was present in 82 (45.6%) patients, LVI was reported in 116 (64.4%) patients, and ETE was seen in 58 (32.2%) patients (Table 1). The accuracy of multifocality by preoperative Ultrasonography (US) check is 92.2% (94/102), while other 8 patients' tumor with small than 5 mm in diameter in histopathology.

Among these 180 PTC patients, CLNM were found in 122 (67.8%) patients with PTC. The comparison of the clinicopathological characteristics between CLNM positive and negative is present in Table 2. It shows that the frequency of CLNM was higher in multifocality ( $p < 0.05$ ), HT ( $p < 0.05$ ) and LVI ( $p < 0.05$ ). However, the comparison of age, gender, tumor size and ETE are not significant between these groups.

In the analysis for risk factor of CLNM with univariate logistic regression analysis, CLNM was significantly correlated with multifocality (OR = 2.796, 95%CI = 1.468–5.323,  $p = 0.002$ ), HT (OR = 5.948, 95%CI = 2.814–12.575,  $p < 0.001$ ) and LVI (OR = 16.029, 95%CI = 7.429–34.585,  $p < 0.001$ ). (Table 3).

Multivariate logistic regression analysis reported that there were independent relationships between CLNM and some significant clinicopathological factors found in the univariate analysis. Some clinicopathological factors such as multifocality, HT and LVI were independently correlated with CLNM. The OR for the associations of

**Table 1**  
Clinicopathologic characteristic of PTC patients.

		n	%
Age	$\geq 45$ years	88	48.9
	$< 45$ years	92	51.1
Gender	male	33	18.3
	female	147	81.7
Size	$> 10$ mm	30	16.7
	$\leq 10$ mm	150	83.3
Multifocality	Yes	102	56.7
	No	78	43.3
HT	Yes	82	45.6
	No	98	54.4
LVI	Yes	116	64.4
	No	64	35.6
ETE	Yes	58	32.2
	No	122	67.8

HT Hashimoto's thyroiditis, LVI lymphovascular invasion, ETE extrathyroidal extension.

**Table 2**

Factors associated with CLNM in PTC.

		CLNM number	P
Age	$\geq 45$ years	58	0.60
	$< 45$ years	64	
Gender	male	25	0.27
	female	97	
Size	$> 10$ mm	17	0.15
	$\leq 10$ mm	107	
Multifocality	Yes	79	$< 0.05$
	No	43	
HT	Yes	71	$< 0.05$
	No	51	
LVI	Yes	102	$< 0.05$
	No	20	
ETE	Yes	38	0.83
	No	84	

HT Hashimoto's thyroiditis, LVI lymphovascular invasion, ETE extrathyroidal extension.

CLNM with multifocality, HT and LVI were 3.346 (95%CI = 1.325–8.912), 10.096 (95%CI = 3.513–29.016), and 25.430 (95%CI = 9.414–69.693), respectively (Table 3).

## 4. Discussion

The incidence of PTC has risen dramatically over last two decades, and PTC patients with CLNM are usually have poor clinical outcome. Increased awareness of thyroid nodular disease, depending on the method of CLNM detection such as US and fine needle aspiration biopsy (FNAB). It has been reported that PCND yield high rates of CLNM [17–19].

At present, there are still controversies on how to optimally manage PTC, and one common debate is whether PCND should be taken in TC including PTC [15,20,21]. The guideline from American Thyroid Association (ATA) recommended that PCND should be considered in patients with advanced primary tumors (T3 or T4) and clinically involved lateral neck nodes (cN1b) that may result in macro-metastases [22]. However, there is no consensus about PCND is needed when CLNM is detected by US. The major reason for the controversy of PCND may include its higher incidence of postoperative complications and may decrease the patients' quality of life [12,23]. Therefore, identification of independent risk factors predicting CLNM would be helpful for surgeons to make an appropriate decision about the necessity of PCND in PTC patients.

At present, we performed a retrospective analysis of 180 PTC patients to identify clinicopathological risk factors predicting CLNM in PTC. Our study found several risk factors predicting CLNM in PTC patients, including multifocality, HT and LVI. Recognition of these risk factors may help identify PTC patients who are at higher risk for harboring metastatic lymph nodes. Our results are somewhat similar to other researches that have detected risk factors of CLNM in PTC patients. However, younger age, male sex, tumor size and ETE were not predictive of CLNM in our study compared to other studies [18,24–27].

Multifocality is considered to be associated with higher rates of CLNM, regional recurrence and poor prognosis in PTC patients [28–30]. Our results revealed that the rate of CLNM was higher in multifocal patients than unifocal patients (64.8% vs. 35.2%,  $p < 0.05$ ). Multivariate analysis revealed multifocality was associated with CLNM in PTC patients. A recent study by Siddiqui et al. observed that multifocality was significantly increased the risk of CLNM in PTC [31]. Similarly, Soyulu et al. reported that CLNM was significantly more likely in PTC patients with multifocality [27]. However, some other studies found that there is no significant association between multifocality and CLNM in PTC [27,32]. The relationship between LVI and CLNM in PTC is also been controversial. Yuan et al. reported that there was no

**Table 3**  
Multivariate logistic regression analysis of CLNM.

Variable	Univariate analysis			Multivariate analysis		
	OR	95% CI	P	OR	95% CI	P
Age	0.846	0.452–1.581	0.600	0.714	0.285–1.789	0.473
Gender	0.621	0.261–1.476	0.281	0.929	0.298–2.894	0.899
Size	0.560	0.251–1.250	0.157	0.730	0.241–2.211	0.578
Multifocality	2.796	1.468–5.323	0.002	3.436	1.325–8.912	0.011
HT	5.948	2.814–12.575	< 0.001	10.096	3.513–29.016	< 0.001
LVI	16.029	7.429–34.585	< 0.001	25.430	9.414–69.693	< 0.001
ETE	0.964	0.495–1.880	0.915	0.841	0.334–2.117	0.714

OR Odds Ratio, CI Confidence Interval, HT Hashimoto's thyroiditis, LVI lymphovascular invasion, ETE extrathyroidal extension.

significant association between LVI and CLNM in PTC patients [4]. Our results showed that LVI was an important predictor of CLNM in PTC patients. These results suggested that more researches of relationship between risk factors and CLNM are needed.

HT is the most common form of autoimmune thyroid disease, and considered to be correlated with thyroid dysfunction and the development of thyroid nodules [33,34]. The relationship between PTC and HT has still been a controversial issue. Some studies have showed HT is a risk factor for PTC, whereas others have not observed the positive correlation [35–37]. Our study implies that HT was a risk factor for CLNM in PTC.

Our study has some limitations. First, the current study was a retrospective study from a single center, there might have been a selection bias. Second, the sample size was not large enough, with only 180 patients being included. Large sample studies are needed to confirm our predictive results. Third, our study was not evaluated the effect of PCND on survival and recurrence of the PTC patients because the follow up time was relatively short.

In conclusion, our results suggested that multifocality, HT and LVI are independent predictors of CLNM in PTC patients. Therefore, these risk factors should be considered by surgeons when deciding whether to perform PCND in PTC patients.

## Ethical approval

Not required.

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None.

## Author contribution

Tang Tong and Li Jia study design and write the article.  
Wen Han and Zheng Lu data analysis.  
Zhang Lei and Shi Jianing data collection.

## Conflicts of interest

None.

## Research registration number

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## Guarantor

Tang Tong.

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