

# Predictive Factors for Level V Lymph Node Metastases in Papillary Thyroid Carcinoma with $BRAF^{V600E}$ Mutation and Clinicopathological Features

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**Background:** Therapeutic lateral neck dissection (LND) is recommended in papillary thyroid carcinoma (PTC) patients with clinically lateral lymph node metastasis (LLNM), whether underwent level V LND remains controversial for lacking of sensitive predicting system.  $BRAF^{V600E}$  mutation is associated with aggressive tumor behavior, recurrence, and disease-specific mortality of PTC. However, the relationship between  $BRAF^{V600E}$  mutation and level V LNM is unclear.

**Methods:** Univariate and multivariate analyses were retrospectively conducted on the potential predictive factors of 252 PTC patients who underwent initial treatment of neck lymph node dissection from September 2015 to October 2018 in our institute.  $BRAF^{V600E}$  mutation and the clinicopathological characteristics of the two groups were compared.

**Results:** LLNM was presented in 208 (82.5%) patients and level II–V LNM was present in 42.8%, 71.2%, 85.1%, 17.8% patients, respectively.  $BRAF^{V600E}$  mutation was observed in 188 (74.6%) patients and was significantly associated with patients' age, lymphocytic thyroiditis, capsule invasion, bilateral central lymph node metastasis (CLNM) and level V LNM in PTC. Univariate analysis revealed that lymphocytic thyroiditis, tumor size, number of CLNM, Level II LNM, Level III LNM, simultaneous Level II+III, simultaneous Level III+IV and simultaneous Level II+III+IV were significantly correlated with Level V LNM. In addition, multivariate analysis revealed that tumor size  $\geq 2.5$  cm, number of CLNM  $\geq 3$ , level II metastases and  $BRAF^{V600E}$  mutation were independent Level V LNM predictors (odds ratio 3.910, 3.660, 8.410, 0.439; 95% CI 1.737–10.135, 1.054–12.713, 1.233–57.355, 0.280–0.827, respectively).

**Conclusion:** In summary, we presented several independent predictive factors for level V LNM in PTC patients. We constructed a risk prediction model consisting of tumor size  $\geq 2.5$  cm, number of CLNM  $\geq 3$  and level II metastases and  $BRAF^{V600E}$  mutation that may guide surgeons to evaluate the nodal status in PTC and perform tailored therapeutic LND.

**Keywords:** papillary thyroid carcinoma,  $BRAF^{V600E}$  mutation, level V lymph nodes metastasis, pathological features

## Introduction

Thyroid cancer is a common endocrine malignancy, and has become the fourth most common malignant cancer in women in China.<sup>1</sup> Papillary thyroid carcinoma (PTC) is the most common subtype of thyroid cancer, influencing the health and quality of life of people worldwide.<sup>2,3</sup> Cervical lymph node metastasis (LNM), a common clinical phenomenon in PTC, is an independent risk factor for local recurrence and PTC-specific mortality.<sup>4,5</sup> Therefore, therapeutic lateral neck

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dissection (LND) is generally recommended in patients with LNM. In general, the extent of therapeutic LND includes level II–V. However, whether routine level V lymphadenectomy in patients with PTC with clinically lateral lymph node metastasis (LLNM) remains controversial.<sup>6</sup> An increasing number of recent studies have shown that the incidence of level V lymph node metastasis is significantly lower than the incidence of level II–IV lymph node metastasis.<sup>7</sup> In addition, level V lymphadenectomy may cause postoperative complications such as shoulder dysfunction, supraclavicular numbness, neuralgia, and sternocleidomastoid muscle atrophy.<sup>8</sup> Thus, an effective therapeutic LND is critical to postoperative outcome. A majority of previous studies had explored some predictors for level V LNM in PTC patients based on clinical and sonographic characteristic. However, not taking the genetic background into consideration makes predicting the evidence of level V LNM less accurate than we clinicians are confused.

The *BRAF*<sup>V600E</sup> mutation has been well known to be the most common oncogenic mutation of PTC, occurring in approximately 45% of patients cases on average.<sup>9</sup> These are well-established *BRAF*<sup>V600E</sup> mutation constitutes to aggressive tumor behavior as well as poor clinical outcomes, including recurrence of PTC, and PTC-specific mortality.<sup>10,11</sup> However, *BRAF*<sup>V600E</sup> mutation related to level V LNM is unclear. Emerging evidence has shown a potential value of *BRAF*<sup>V600E</sup> mutation in predicting central cervical lymph node metastasis of PTC.<sup>12,13</sup> Given these data, in this retrospective study, we tested our hypothesis that *BRAF*<sup>V600E</sup> mutation might constitute a genetic background conferring LNM and that BRAF status could thus differentiate the prognostic risk of level V LNM in PTC.

## Methods

### Study Population

This work obtained approval to retrospectively review the medical records of patients from the Ethics Committee of Xiangya Hospital, Central South University (approval number, 2019030440), and conducted in accordance with the Declaration of Helsinki. Written informed consent for the evaluation of *BRAF*<sup>V600E</sup> mutation status was obtained from every participant patient prior to thyroidectomy. In addition to approving the study protocol, the Ethics Committee required neither patient approval nor informed consent for the review of records. Furthermore, we confirmed that the data related to this manuscript were anonymized.

We retrospectively reviewed the medical records of consecutive patients with PTC who underwent simultaneous total thyroidectomy (TT), bilateral central neck dissection (CND), and LND (at least from levels II to V) at the department of General Surgery, Xiangya Hospital, Central South University between September 2015 and October 2018. Patients were excluded if they had (a) a previous history of thyroidectomy or (b) refusal of *BRAF*<sup>V600E</sup> mutation analysis or (c) absent or insufficient ultrasonography image or (d) other subtypes of thyroid carcinoma. As a result, a total of 252 patients were enrolled in this study. Almost all patients were from central China, and most of them were from Hunan Province.

Before operation, all patients underwent preoperative physical examination, high-quality thyroid ultrasonography (US), and US-guided fine-needle aspiration biopsy (USgFNAB) of the primary tumor. The final diagnosis of primary tumors and cervical LNM was based on pathological examination of surgical specimens by two separate pathologists. In this study, lateral neck nodes were classified into neck levels (II to V) based on the criteria of the American Head and Neck Society.<sup>14</sup> In addition, *BRAF*<sup>V600E</sup> mutation status was determined after surgical and medical treatments in all patients and did not affect decision making regarding treatments. We isolated genomic DNA from primary PTC tumors and analysed the sequence of exon 15 of BRAF gene for V600E mutation according to published studies.<sup>15</sup>

### Statistical Analysis

Risk factors including *BRAF*<sup>V600E</sup> mutation status, sex, age, thyroid-stimulating hormone (TSH) level, lymphocytic thyroiditis, tumor size, capsular invasion, ultrasound findings (including location, solid component, shape, margin, echogenicity, calcifications), and the extent of LNM were obtained and analyzed in this study.

In univariate analysis, categorical variables were analyzed using Pearson's chi-square test and continuous variables were analyzed using the Student's *t*-test or the Wilcoxon rank-sum test. Besides, we performed receiver-operating characteristic (ROC) curve analysis to determine the optimal cut-off points for patient age, tumor size, and number of central lymph node metastasis (CLNM) as well as to test the accuracy of those continuous variables in predicting level V lymph node metastasis. The area under the curve (AUC) > 0.700 was considered to be meaningful. At last, a binary logistic regression model was used to evaluate the risk factors for level V lymph node metastasis

in PTC. SPSS software (version 22.0; SPSS, Chicago, IL) was used for these analyses. All *p*-values were two sided, and a value  $\leq 0.05$  was considered significant.

## Results

### Demographic Variables

As summarized in (Table 1), a total of 252 patients with PTC, of whom 69.8% (176) were women and 30.2% (76) were men, were included in the study, with a median age

**Table 1** Demographics and Clinical Characteristics of 252 Solitary Papillary Thyroid Carcinoma Patients

Characteristics	Results (%)
No. of patients	252
Sex	
Male	76(30.2)
Female	176(69.8)
Age (mean and range)	39.6 ± 11.9 (12 to 72)
≥55	23(9.1)
<55	229(90.9)
<i>BRAF</i> <sup>V600E</sup> mutation	188(74.6)
TSH levels	
Low	6(2.4)
Normal	209(82.9)
High	37(14.7)
Lymphocytic thyroiditis	89(35.3)
Tumor size (cm, mean)	1.981 ± 1.246
≥1.0	212(84.1)
<1.0	40(15.9)
Calcification of the tumor on neck US	233(92.5)
Multifocality	
Yes/No	125(49.6)/127(50.4)
Bilaterally	
Yes/No	91(36.1)/161(63.9)
Capsule invasion	69(27.4)
CLNM (mean)	205(81.3)/(4.286 ± 4.524)
Ipsilateral	204(80.9)
Contralateral	24(9.5)
Bilateral	55(21.8)
LLNM	208(82.5)
Level II	89(42.8)
Level III	148(71.2)
Level IV	177(85.1)
Level V	37(17.8)

**Abbreviations:** TSH, thyroid-stimulating hormone; US, ultrasonography; CLNM, central lymph node metastases; LLNM, lateral lymph node metastasis.

of 39.6±11.9 years (range, 12 to 72) at diagnosis of PTC and 229 (90.9%) were younger than 55 years. There were 43 patients with thyroid dysfunction (6 hyperthyroidisms and 37 hypothyroidisms, respectively) and 89 patients with lymphocytic thyroiditis. *BRAF*<sup>V600E</sup> mutation was observed in 188 (74.6%) patients. Suspicious ultrasonography features including solid component, echogenicity, calcification, and irregular/lobulated margins were examined, calcification was observed in 233 (92.5%) patients.

In our study, LNM was histologically confirmed to involve the central compartment (CLNM) in 205 patients (81.3%) and the lateral compartment (LLNM) in 208 patients (82.5%). Out of the 205 patients with CLNM, the mean ± SD (Standard Deviation) number of metastatic lymph nodes was 4.286±4.524 and 204 patients (80.9%) had LNM in the central compartment ipsilateral to the primary tumor. 24 (9.5%) had LNM in the contralateral central compartment and 55 (21.8%) had LNM in the bilateral central compartments. Out of 208 patients with LLNM, Level IV metastases were most common (177/208; 85.1%), followed by level III (148/208; 71.2%), level II (89/208; 42.8%), and level V (37/208; 17.8%) metastases.

### *BRAF*<sup>V600E</sup> Mutation Is Associated with Multiple Clinicopathological Features Including Level V Lymph Node Metastasis

To understand the relationship between *BRAF*<sup>V600E</sup> mutation and clinicopathological features, univariate analysis was conducted. We found that *BRAF*<sup>V600E</sup> mutation was associated with age, lymphocytic thyroiditis, capsule invasion, LNM in the bilateral central compartments and Level V lymph node metastasis (*p* < 0.05). The mean ± SD of age in *BRAF*<sup>V600E</sup> mutation group was significantly higher than in wild group (40.755±11.407 vs 36.031±12.520, *p* < 0.01). Similarly, capsule invasion was easier to happen in *BRAF*<sup>V600E</sup> mutation group (which) was significantly higher than in wild group (31.4% vs 15.6%, *p* < 0.01). Moreover, patients with lymphocytic thyroiditis were more common in *BRAF* wild group than in *BRAF*<sup>V600E</sup> mutation group (51.6% vs 29.8%, *p* < 0.01). Also, we found that patients with wild *BRAF* status were observed with higher risk of bilateral CLNM (31.3% vs 18.6%, *p* < 0.01) and Level V lymph node metastasis (25.0% vs 11.2%, *p* < 0.01). That is to say, *BRAF*<sup>V600E</sup> mutation could be a protective factor for Level V LNM in PTC patients. Detailed information is shown in (Table 2).

**Table 2** Associations Between *BRAF*<sup>V600E</sup> Mutation and Clinicopathological Characteristics in PTC

Parameter	<i>BRAF</i> <sup>V600E</sup> Mutation Status		P-value
	Mutation, n (%)	Wild, n (%)	
Total	188(74.6)	64(25.4)	
Female	133(70.7)	43(67.2)	0.592
Age (Mean ± SD)	40.755±11.407	36.031±12.520	<b>0.006<sup>a</sup></b>
≥55	17(9.0)	6(9.4)	0.936
<55	171(91.0)	58(90.6)	
TSH levels			
Low	3(1.6)	3(4.7)	0.110
Normal	161(85.6)	48(75.0)	
High	24(12.8)	13(20.3)	
Lymphocytic thyroiditis	56(29.8)	33(51.6)	<b>0.002<sup>b</sup></b>
Tumor size (Mean ± SD, cm)	1.964±1.288	2.031±1.123	0.711
>1.0	58(30.9)	25(39.1)	0.227
≤1.0	130(69.1)	39(60.9)	
Location			
Left lobe	58(30.9%)	13(20.3%)	0.056
Right lobe	59(31.3%)	32(50.0%)	
Isthmus	9(4.8%)	1(1.6%)	
Bilateral	62(33.0%)	18(28.1%)	
Solid component on neck US			
Pure solid	183(97.3)	61(95.3)	0.424
Echogenicity of the tumor on neck US			
Hypoechoic	166(88.3)	57(89.1)	0.868
Margin of the tumor on neck US			
Smooth	54(28.7)	16(25.0)	0.566
Ill-defined margin	134(71.3)	48(75.0)	
Calcification of the tumor on neck US	172(91.5)	61(95.3)	0.317
Multifocality	96(51.1)	29(45.3)	0.427
Capsule invasion	59(31.4)	10(15.6)	<b>0.015<sup>b</sup></b>
Bilateral tumor	71(37.8)	20(31.3)	0.349
CLNM	149(79.3)	56(87.5)	0.144
Ipsilateral	148 (78.7)	56 (87.5)	0.143
Contralateral	16(8.5)	8(12.5)	0.348
Bilateral	35(18.6)	20(31.3)	<b>0.035<sup>b</sup></b>
CLNM number (Mean ± SD)	3.894±3.893	5.438±5.896	0.054

(Continued)

**Table 2** (Continued).

Parameter	<i>BRAF</i> <sup>V600E</sup> Mutation Status		P-value
	Mutation, n (%)	Wild, n (%)	
LLNM	155(82.4)	53(82.8)	0.947
Level II	62(33.0)	27(42.2)	0.183
Level III	106(56.4)	42(65.6)	0.195
Level IV	130(69.1)	47(73.4)	0.517
Level V	21(11.2)	16(25.0)	<b>0.007<sup>b</sup></b>

**Notes:** Variables with statistical significance were shown in bold. <sup>a</sup>The Student's t-test was adopted. <sup>b</sup>The Wilcoxon rank-sum test was adopted.

**Abbreviations:** PTC, papillary thyroid carcinoma; SD, Standard Deviation; TSH, thyroid-stimulating hormone; US, ultrasonography; CLNM, central lymph node metastases; LLNM, lateral lymph node metastasis.

### Distribution of Level V Lymph Node Metastasis Among PTC Patients with Different Clinicopathological and Ultrasonography Features

As shown in (Table 3), we did not find any significant association between level V LNM and sex, age, TSH levels, ultrasonography features. However, patients with lymphocytic thyroiditis appeared to have a higher prevalence of level V LNM than those without (51.4% vs 32.6%,  $p < 0.05$ ) and the mean size of the primary tumor in patients with level V LNM was larger than that in patients without level V LNM (mean ± SD: 2.695±1.185 vs 1.859±1.217,  $p < 0.05$ ). Since in ROC analysis, we found the optimal cutoff tumor size between the two groups was 2.45 cm, so, we took 2.5 cm as the cut-off value of tumor size in the following Univariate analysis and Multivariate analysis. We found patients with tumor size >2.5 have a higher prevalence of level V LNM (64.9% vs 35.1%,  $p < 0.001$ ).

CLNM was observed significantly related to the prevalence of level V LNM, especially in patients with contralateral CLNM and bilateral CLNM ( $p < 0.01$ , both). Besides, the number of CLNM in patients with level V LNM was significantly bigger than those without level V LNM ( $p < 0.01$ ). Univariate analysis also showed that the presence of level V LNM was significantly associated with Level II, Level III, and simultaneous Level II+III, Level III+IV and Level II+III+IV lymph node metastases.

### Multivariate Logistic Analysis for Level V LNM of PTC

To define the predictors of level V LNM of PTC, we performed binary logistic regression analyses with

**Table 3** Univariate Analysis of Risk Factors Related to Level V Lymph Node Metastasis in PTC

Parameter	Level V Lymph Node Metastases		P-value
	Present, n (%)	Absent, n (%)	
Total	37(14.7)	215(85.3)	
Sex			
Male	14(37.8)	62(28.8)	0.271
Female	23(62.2)	153(71.2)	
Age (Mean ± SD)	37.811±14.966	39.856±11.248	0.432 <sup>a</sup>
≥55	4(10.8)	19(8.8)	0.700
<55	33(89.2)	196(91.2)	
TSH levels			
Low	2(5.4)	4(1.9)	0.052
Normal	25(67.6)	184(85.6)	
High	10(27.0)	27(12.6)	
Lymphocytic thyroiditis	19(51.4)	70(32.6)	<b>0.027<sup>b</sup></b>
Tumor size (Mean ± SD, cm)	2.695±1.185	1.859±1.217	< <b>0.001<sup>a</sup></b>
≤2.5	13(35.1)	156(72.6)	< <b>0.001<sup>b</sup></b>
>2.5	24(64.9)	59(27.4)	
Pure solid on neck US	35(94.6)	209(97.2)	0.402
Echogenicity of the tumor on neck US			
Hypoechoic	31(83.8)	192(89.3)	0.331
Smooth margin of the tumor on US	31(83.8)	151(70.2)	0.089
Calcification of the tumor on neck US	37(100)	196(91.2)	0.060
Multifocality	21(56.8)	104(48.4)	0.346
Capsule invasion	11(29.7)	58(27.0)	0.729
Bilateral tumor	15(40.5)	76(35.3)	0.544
CLNM	35(94.6)	170(79.1)	<b>0.025<sup>b</sup></b>
Ipsilateral	34 (79.1)	170 (91.9)	0.067
Contralateral	8(21.6)	16(7.4)	<b>0.007<sup>b</sup></b>
Bilateral	15(40.5)	40(18.6)	<b>0.003<sup>b</sup></b>
Number of CLNM (Mean ± SD)	7.649±6.845	3.707±3.713	<b>0.002<sup>a</sup></b>
LLNM	37(100)	171(79.5)	<b>0.002<sup>b</sup></b>
Level II	25(67.6)	64(29.8)	< <b>0.001<sup>b</sup></b>
Level III	32(86.5)	116(54.0)	< <b>0.001<sup>b</sup></b>
Level IV	29(78.4)	148(68.8)	0.241
Level II+III	21(56.8)	52(24.2)	< <b>0.001<sup>b</sup></b>
Level III+IV	26(70.3)	92(42.8)	<b>0.002<sup>b</sup></b>
Level II+III+IV	17(45.9)	44(20.5)	<b>0.001<sup>b</sup></b>

**Notes:** Variables with statistical significance were shown in bold. <sup>a</sup>The Student's t-test was adopted; <sup>b</sup>The Wilcoxon rank-sum test was adopted.

**Abbreviations:** PTC, papillary thyroid carcinoma; SD, standard deviation; TSH, thyroid-stimulating hormone; US, ultrasonography; CLNM, central lymph node metastases; LLNM, lateral lymph node metastasis.

**Table 4** Multivariate Analysis of Risk Factors Related to Level V Lymph Node Metastasis in PTC

Variables	OR	95% CI	P-value
<i>BRAF</i> <sup>V600E</sup> mutation	0.439	0.280–0.827	<b>0.027</b>
Lymphocytic thyroiditis	0.032	0.878–4.703	0.098
Tumor size ≥2.5 cm	3.910	1.737–10.135	<b>0.001</b>
Present of CLNM	0.923	0.136–6.278	0.934
Number of CLNM≥3	3.660	1.054–12.713	<b>0.041</b>
Contralateral CLNM	2.395	0.776–7.391	0.129
Bilateral CLNM	0.892	0.298–2.665	0.837
Level II metastasis	8.410	1.233–57.355	<b>0.030</b>
Level III metastasis	7.648	0.785–63.832	0.060
Level II+III metastases	0.752	0.053–10.634	0.832
Level III+IV metastases	1.210	0.193–7.592	0.839
Level II+III+IV metastases	0.162	0.015–1.734	0.132

**Note:** Variables with statistical significance were shown in bold.

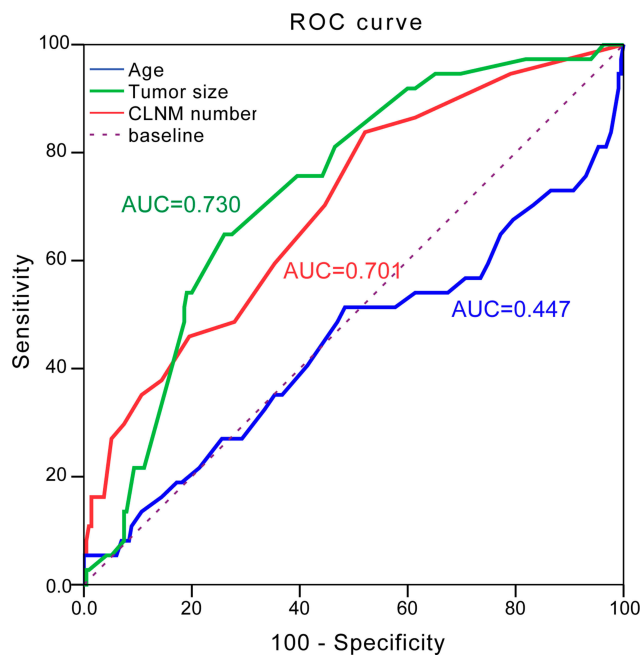
**Abbreviations:** PTC, papillary thyroid carcinoma; OR, odds ratio; 95% CI, 95% confidence interval; CLNM, central lymph node metastases;

*BRAF*<sup>V600E</sup> mutation status and clinicopathologic features (Table 4). In our result, we found that *BRAF*<sup>V600E</sup> mutation was statistically significant and associated with level V LNM (OR =0.439, 95% CI, 0.280–0.827, *p* =0.027). However, tumor size ≥2.5 cm (OR =3.910, 95% CI, 1.737–10.135, *p* =0.001), the number of CLNM≥3 (OR =3.660, 95% CI, 1.054–12.713, *p* =0.041) and level II LNM (OR =8.410, 95% CI, 1.233–57.355, *p* =0.030) turned out to be independent risk factors associated with level V LNM. Besides, coexisting lymphocytic thyroiditis, presence of CLNM, contralateral CLNM, bilateral CLNM, Level III metastasis, simultaneous Level II+III metastases, simultaneous Level III+IV metastases and simultaneous Level II+III+IV metastases were not found to be associated with level V LNM.

## Association Between Risk Factors and Level V Lymph Node Metastasis in the Score System

Finally, we computed a risk score for each patient based on age, tumor size and the number of CLNM and constructed a ROC curve using the risk score. In our result, the area under the curve of tumor size and CLNM number were 0.730 and 0.701, respectively, which implied to be well predictors of level V LNM. Moreover, when set cut-off point of 2.45cm of tumor size and cut-off point of 2.5 of CLNM number resulted in a sensitivity of 64.9%, specificity of 74.0% (positive predictive value (PPV)=30.0%, negative predictive value (NPV)=92.4%, and accuracy =72.6%) and cut-off point of 2.5 of CLNM number in





**Figure 1** Receiver operating characteristic (ROC) curve for age (blue line), tumor size (green line) and CLNM number (red line) in the prediction of level V LNM in PTC. **Abbreviations:** LNM, lymph node metastases; CLNM, central lymph node metastasis; AUC, area under curve.

a sensitivity of 83.8% and a specificity of 47.9% (PPV=21.7%, NPV=94.5%, and accuracy =53.2%) for predicted level V LNM, respectively. However, no significant relationship was observed between patient age and level V LNM (Figure 1).

## Discussion

This study is the first study evaluating both clinicopathological features and genetic background for predicting level V LNM in PTC patients. We identified four suspicious features significantly associated with level V LNM of PTC: *BRAF*<sup>V600E</sup> mutation, tumor size  $\geq 2.5$  cm, number of CLNM  $\geq 3$  and level II metastasis. According to our results, among those predictors, we firstly observed that *BRAF*<sup>V600E</sup> mutation carriers (OR =0.439, 95% CI, 0.280–0.827,  $p =0.027$ ) were less likely to present level V LNM. While, as the number of other predictors (tumor size  $\geq 2.5$  cm, number of CLNM  $\geq 3$  and level II metastases) increased, the possibility of level V LNM of PTC also significantly increased. According to published studies, the ability to detect *BRAF*<sup>V600E</sup> mutation in FNAB cytologic specimens is not inferior to that in postoperative pathological specimens,<sup>16</sup> which means *BRAF*<sup>V600E</sup> mutation would be considered as a preoperative predictive factor for occult level V LNM of PTC patients.

Nowadays PTC belongs to the low-risk cancer with rarely life-threatening; however, the presence of LNM significantly increases the risk of locoregional recurrence.<sup>17</sup> Emerging evidences have demonstrated decreased disease-free survival rate and increased mortality associated with regional LNM.<sup>18</sup> Even though lots of novel methods were emerging to target cancer cells and LNM of PTC,<sup>19</sup> LND is generally recommended in PTC patients with LNM. However, the extensive postoperative complications caused by LND should not be ignored which will reduce the quality of life of patients. Therefore, determining a rational extent of therapeutic LND is vital. Whether level V should be included in therapeutic LND continues to be controversial. Therefore, we analyzed the frequency and the risk factors for level V LNM in PTC with clinically LLNM to determine the rational extent of therapeutic LND.

Currently, the methods used to diagnose LNM include computed tomography (CT), magnetic resonance imaging (MRI), and ultrasound imaging. In our study, the preoperative US characteristics we collected were not statistically related to level V LNM, which is consistent with the previous studies by Yang et al.<sup>6</sup> Therefore, preoperative US cannot effectively predict the presence of level V LNM. The new technology Ultrasound-guided fine needle aspiration cytology (USgFNAC) is recommended as the gold standard used in the diagnosis of PTC lymph node metastasis.<sup>20</sup> Although USgFNAC was showed to be the most specific and accurate imaging modality to detect cervical LNM, the latest research reported that the false-negative rate of USgFNAC could be as high as 45–52%, which has a relatively lower sensitivity than US.<sup>21</sup> In addition, given the closer relationship of the node to the surrounding vascular structures, routine preoperative USgFNAC is not done to guide LND at most institutions including ours. Besides, there were studies reported the association between clinicopathological and ultrasonography features and the risk of having positive LLNM or level V LNM,<sup>6</sup> however, seldom their genetic backgrounds are taken into consideration. Like other cancers, PTC is a genetically driven disease and mutation of the *BRAF* gene is common in PTC. In this study, patients with *BRAF*<sup>V600E</sup> mutation accounted for 74.6% of PTC patients, consistent with the previous reports (occurring more than 45% of patient cases).<sup>15</sup> Over the last decade, the relationship between *BRAF*<sup>V600E</sup> mutation and clinicopathological characteristics in PTC has been well studied. *BRAF*<sup>V600E</sup> mutation could lead to an increase in tumor recurrence and

cancer-related mortality.<sup>22,23</sup> As expected, *BRAF*<sup>V600E</sup> mutation was confirmed to be significantly related to patients' age, lymphocytic thyroiditis, capsule invasion, bilateral CLNM and level V LNM in PTC in our study but the phenomenon we observed that *BRAF*<sup>V600E</sup> mutation seems to be a protection factor of level V LNM needs further investigations.

Several previous studies have indicated that, in patients with PTC and clinical LNM, most LLNM were levels II, III, and IV. Almost consistent with previous studies, we found that LLNM mainly occurred at levels II, III, and IV with frequencies of 35.3%, 58.7%, and 70.2%, respectively. We also found the number of CLNM and level II metastasis in PTC are indications for increased risk level V LNM. In addition, we observed that tumor size $\geq 2.5$  cm presented a 3.91-fold increased risk of level V LNM in PTC patients. Consistent to previous studies, Zhou et al found that tumor size $>7$  mm was a risk factor of CLNM and another report also demonstrated that larger tumor size of PTC enhanced tumor aggressiveness and worsened survival of patients.<sup>24,25</sup>

There are some potential limitations to our study. Because this was a retrospective observational study and there might be selection bias. Moreover, the 252 patients of this study are all Chinese, and whether the identified factors can predict level V LNM in other races needs further investigation. Furthermore, several risk factors for level V LNM such as family history, behavior and Tg level have not been investigated in our study.

## Conclusion

In summary, we presented several independent predictive factors for level V LNM in PTC patients. We constructed a risk prediction model consisting of tumor size  $\geq 2.5$  cm, number of CLNM $\geq 3$  and level II metastasis and *BRAF*<sup>V600E</sup> mutation that may guide surgeons to evaluate the nodal status in PTC and perform tailored therapeutic LND.

## Abbreviations

PTC, papillary thyroid carcinoma; LNM, lymph node metastasis; LND, lateral neck dissection; LLNM, lateral lymph node metastasis; CND, central neck dissection; TT, total thyroidectomy; US, ultrasonography; USgFNAB, US-guided fine-needle aspiration biopsy; TSH, thyroid-stimulating hormone; ROC, receiver operating characteristic; CLNM, central lymph node metastasis; AUC, area under the curve; SD, Standard Deviation; CT, computed tomography; MRI, magnetic resonance imaging; USgFNAC, Ultrasound-

guided fine needle aspiration cytology; CI, confidence interval; PPV, positive predictive value; NPV, negative predictive value; OR, odds ratio.

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## Disclosure

The authors declare that they have no competing interests in this work.

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