



# Risk factors for cervical lymph node metastasis at different lateral levels in papillary thyroid cancer: level III as the central hub

Yu Zhang<sup>1,2#</sup>, Xiaoyu Ji<sup>3#</sup>, Xialing Zhang<sup>4</sup>, Yu Wang<sup>1,2</sup>

<sup>1</sup>Department of Head and Neck Surgery, Fudan University Shanghai Cancer Center, Shanghai, China; <sup>2</sup>Department of Oncology, Shanghai Medical College, Fudan University, Shanghai, China; <sup>3</sup>Department of Oncology, Huashan Hospital, Fudan University, Shanghai, China; <sup>4</sup>Department of Pathology, Huashan Hospital, Fudan University, Shanghai, China

**Contributions:** (I) Conception and design: Y Zhang, Y Wang; (II) Administrative support: Y Wang, X Zhang; (III) Provision of study materials or patients: Y Wang; (IV) Collection and assembly of data: Y Zhang, X Ji; (V) Data analysis and interpretation: Y Zhang, X Ji; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

<sup>#</sup>These authors contributed equally to this work.

**Correspondence to:** Yu Wang, MD, PhD. Department of Head and Neck Surgery, Fudan University Shanghai Cancer Center, 7W of No. 3 Building, No. 270 Dong'an Road, Shanghai 200030, China; Department of Oncology, Shanghai Medical College, Fudan University, Shanghai, China. Email: neck130@sina.com; Xialing Zhang, MS. Department of Pathology, Huashan Hospital, Fudan University, 2W of No. 11 Building, No. 12 Middle Wulumuqi Road, Shanghai 200040, China. Email: zhangxialing2014@163.com.

**Background:** As the most prevalent histological type of thyroid cancer, the prognosis of papillary thyroid cancer (PTC) is closely related to cervical lymph node metastasis (LNM), particularly in the case of lateral LNM (LLNM). The patterns of cervical LNM in PTC remain inconclusive. We aim to assess the risk factors for LLNM and extranodal extension (ENE) at different lateral levels in N1b PTC patients.

**Methods:** A total of 486 PTC patients with pathologically diagnosed N1b, who underwent thyroidectomy with central and lateral neck lymph node dissection at our hospital between January 2019 and December 2021, were retrospectively retrieved. The metastatic status of different lateral levels was recorded. Further correlation analysis was conducted.

**Results:** Based on the correlation analysis, binary logistic regression analysis indicated that upper location [odds ratio (OR) = 3.067;  $P < 0.001$ ; 95% confidence interval (CI): 2.075–4.534] and central LNM-ENE (CLNM-ENE) (OR = 2.036;  $P = 0.04$ ; 95% CI: 1.044–3.970) are predictive factors for level II metastasis. Additionally, upper location (OR = 2.106;  $P < 0.001$ ; 95% CI: 1.404–3.159) and CLNM (OR = 2.664;  $P < 0.001$ ; 95% CI: 1.681–4.222) were found to be predictive factors for level III metastasis. LLNM at level IV was closely associated only with CLNM. Level III-ENE (OR = 2.347;  $P = 0.03$ ; 95% CI: 1.065–5.176) was found to be highly correlated with level V metastasis. As for ENE, level III-ENE was found to be a risk factor for ENE in all other levels (II, IV, V), while ENE in the other lateral cervical regions also increased the risk for level III.

**Conclusions:** Despite some uncertainties, LLNM remains closely associated with the upper location of PTC. Meanwhile, level III functions as the hub of the lateral neck, with level III-ENE increasing the risk of LLNM in level V, and significantly raising the probability of ENE in other lateral cervical regions. LLNM have its inherent patterns, as evidenced in the study, but also have a degree of unpredictability, therefore an accurate preoperative assessment is essential.

**Keywords:** Papillary thyroid cancer (PTC); lateral lymph node metastasis (LLNM); extranodal extension (ENE); upper location; level III

Submitted Jul 15, 2024. Accepted for publication Nov 06, 2024. Published online Nov 26, 2024.

doi: 10.21037/gs-24-299

View this article at: <https://dx.doi.org/10.21037/gs-24-299>

## Introduction

Papillary thyroid cancer (PTC) is the most prevalent histological type of thyroid cancer and is frequently associated with regional cervical lymph node metastasis (LNM) at the time of initial diagnosis (1). Regional metastasis typically occurs first in the central neck compartment, followed by spread to the lateral compartment. N1b classification is defined by metastasis to the lateral cervical, retropharyngeal, or superior mediastinal lymph nodes (2,3). Lateral LNM (LLNM) is associated with a worse prognosis compared to central LNM (CLNM), exhibiting a higher recurrence rate and reduced disease-free survival (DFS). Some surgeons agreed that therapeutic lateral neck dissection (LND), particularly modified radical neck dissection (MRND), is necessary for N1b PTC patients to enhance regional control rates (4,5).

“Berry picking”, a procedure involving the selective removal of only enlarged or suspicious lymph nodes, is no longer recommended as it has been linked to a high recurrence rate (6,7). The 2015 American Thyroid Association guidelines advocate for compartmental node dissection in cases of LLNM due to the associated risks of recurrence and mortality (8). The MRND is considered by some viewpoints to be a more suitable treatment for patients with lateral cervical LNM from PTC. This procedure

involves the removal of all lateral lymph nodes (LLNs), including levels II to V, while preserving the internal jugular vein, sternocleidomastoid muscle, and spinal accessory nerve (9). The balance between the benefits and risks of different extents of neck dissection is a crucial issue in the surgical treatment of thyroid cancer, considering that the risk of PTC metastasis to levels II and V is relatively low and that clearing lymph nodes in these areas may increase the risk of surgical complications for patients (10,11).

The patterns and pathways of cervical LNM in thyroid cancer remain inconclusive. Current clinical practice generally posits that metastasis initially involves the central compartment lymph nodes, followed by those in the anatomically adjacent levels III and IV. Lymph nodes in levels II and V, which have a lower metastasis rate, tend to be affected later (12-14). In this study, we comprehensively analyzed the characteristics and associated risk factors of LLNM and extranodal extension (ENE) in 486 PTC patients with N1b. Our findings preliminarily indicate potential pathways of LLNM, particularly highlighting the pivotal role of level III lymph nodes as a central hub in the lateral neck. Metastasis and ENE in level III lymph nodes were identified as important risk factors for metastasis in level V, and were significantly associated with ENE in all other lateral cervical lymph nodes. We present this article in accordance with the STROBE reporting checklist (available at <https://gs.amegroups.com/article/view/10.21037/gc-24-299/rc>).

### Highlight box

#### Key findings

- An upper location predicts level II and III metastasis.
- Central lymph node metastasis-extranodal extension (ENE) heightens the risk of level II metastasis and the occurrence of ENE in level II/IV.
- Gross extrathyroidal extension notably increases the likelihood of level IV-ENE.

#### What is known and what is new?

- It is known that level III ENE increases the risk of level V metastasis and ENE in other regions. Additionally, ENE in any region increases the likelihood of level III ENE.
- Level III serves as a central hub in the lateral neck, highlighting its significance in lateral lymph node metastasis (LLNM) in papillary thyroid cancer.

#### What is the implication, and what should change now?

- LLNM exhibit inherent patterns, as demonstrated in the study, but also possess a degree of unpredictability. Therefore, a precise preoperative assessment is crucial.
- Prospective studies on surgical approaches for LLNM are urgently needed to provide evidence-based support.

## Methods

### Patients

A retrospective study was carried out at Fudan University Shanghai Cancer Center (FUSCC) from January 2019 to December 2021. A total of 486 consecutive PTC patients who met the inclusion and did not meet the exclusion criteria were included in the study. The study was approved by the Ethics Committee of FUSCC (No. 050432-4-2307E) and informed consent was obtained from all participants. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

The inclusion criteria were: (I) histopathologically confirmed PTC and LLNM, with preoperative evaluations [including physical examination, high-resolution ultrasonography, computed tomography (CT), and fine needle aspiration biopsy] suggesting suspected LLNM; (II) the treatment involved thyroidectomy combined with central lymph node dissection (CLND) and level II–V LLN dissection; and

(III) complete clinical and pathological records available. The exclusion criteria: (I) other histological types of thyroid cancer; (II) distant metastasis; (III) previous history of thyroid cancer; (IV) presence of other extrathyroidal malignancies; (V) history of head and neck radiation therapy. All participants underwent ultrasound-guided fine-needle aspiration biopsy (UG-FNAB) several weeks before surgery. Tumor morphology-related ultrasound (US) data, including microcalcifications, were collected through ultrasonography performed by two experienced radiologists performing at least 500 neck US/year for thyroid tumors. Post-surgery, diagnosis confirmation and assessment of histopathological features were carried out by two experienced thyroid tumor pathologists.

### *Surgical approach and histopathological analysis*

The condition of the lymph nodes was evaluated using high-resolution neck US or enhanced cervical CT prior to surgery. Additionally, FNAB was conducted on suspected thyroid nodules or cervical lymph nodes to verify the histopathological diagnosis before the surgery. The surgery started with thyroidectomy and CLND, followed by an LND. The CLND encompassed the area from the hyoid bone at the top to the innominate vein at the bottom, and extended laterally to the carotid sheaths, including the prelaryngeal, pretracheal, and paratracheal regions. Therapeutic LND was performed only in patients with clinically suspected LLNM, targeting lymph nodes in the lateral neck across levels II to V. The neck regions were categorized as follows: level II extended from the base of the skull to the lower edge of the hyoid bone; level III was situated between the hyoid bone and the lower border of the cricoid cartilage; level IV ranged from the lower edge of the cricoid cartilage to the clavicle; and level V stretched from the intersection of the sternocleidomastoid and trapezius muscles to the clavicle. A low collar arc-shaped incision is usually selected, extending toward the corresponding side of the neck. For patients with larger tumors, a higher risk of nerve involvement, and preoperative evaluation showing reduced vocal cord activity, intraoperative neuromonitoring (IONM) is considered. Intraoperative frozen pathology examination of the thyroid and tumor lesions is performed. Indocyanine green (ICG) is not routinely used.

### *Clinicopathological variables evaluated*

Data on clinical and pathological characteristics were collected,

including age, sex, tumor size, total tumor size (sum of all tumor diameters for multifocality), extrathyroidal extension (ETE), tumor location, unifocality/multifocality, presence of Hashimoto's thyroiditis (HT), presence of nodular goiter, tumor margin smoothness, presence of microcalcifications, CLNM, and LLNM and ENE at specific level II–V.

### *Statistical analysis*

Data management and statistical analyses were performed using IBM SPSS Statistics for Windows, Version 21.0 (IBM Corp.). Spearman correlation analysis was employed to investigate the relationship between various clinicopathological factors and LLNM, as well as associated ENE, across levels II to V. Variables that exhibited statistically significant P values in the Spearman correlation analysis, as well as those with evident clinical relevance, were included in the binary logistic regression analysis for further assessment. Binary logistic regression was used to examine the association between risk factors and LLNM with ENE at each level. The odds ratio (OR) and 95% confidence interval (CI) were ultimately obtained for each potential risk factor. A P value of less than 0.05 was considered statistically significant.

## **Results**

### *Demographics and clinicopathological characteristics of PTC patients with LLNM*

The preoperative US and enhanced cervical CT showed that 256 cases (52.7%) were suspected of having CLNM, sonographer identified the lateral cervical lymph nodes with the most obvious malignant features and performed biopsies, and all patients were suspected of having lateral cervical LNM before surgery. The clinicopathological characteristics of the 486 patients are presented in *Table 1*. Of the 486 PTC patients with LLNM who received unilateral LND, 188 men (38.7%) and 298 women (61.3%), with a mean age of  $44.80 \pm 13.18$  years. Patients younger than 55 years comprised 416 (85.6%) of the cohort, while those aged 55 years and older accounted for 70 (14.4%). The mean primary tumor and total tumors sizes were  $1.5 \pm 1.0$  and  $1.9 \pm 1.4$  cm, respectively. Characteristics of multifocality and ETE were observed in 206 (42.4%) and 157 (32.3%) of the patients, respectively. HT was found in 160 patients (32.9%), and nodular goiter was present in 121 patients (24.9%). Tumors were observed in 239 (49.2%), 160 (32.9%), and 87 (17.9%) patients in the upper, middle, and lower poles, respectively.

**Table 1** Clinicopathologic characteristics of patients

Variables	Values
Gender	
Female	298 (61.3)
Male	188 (38.7)
Tumor size (cm)	1.5±1.0
Total tumor size (cm)	1.9±1.4
Age (years)	
<55	416 (85.6)
≥55	70 (14.4)
Location	
Upper	239 (49.2)
Middle	160 (32.9)
Lower	87 (17.9)
Multifocality	
Yes	206 (42.4)
No	280 (57.6)
Coexistent HT	
Yes	160 (32.9)
No	326 (67.1)
Coexistent NG	
Yes	121 (24.9)
No	365 (75.1)
Micro ETE	
Yes	131 (27.0)
No	355 (73.0)
Gross ETE	
Yes	26 (5.3)
No	460 (94.7)
Margin	
Smooth	121 (24.9)
Ill-defined	365 (75.1)
Microcalcification	
Yes	352 (72.4)
No	134 (27.6)
CLNM	
Yes	381 (78.4)
No	105 (21.6)

**Table 1** (continued)**Table 1** (continued)

Variables	Values
Level II	
Positive	241 (49.6)
Negative	245 (50.4)
Level III	
Positive	333 (68.5)
Negative	153 (31.5)
Level IV	
Positive	354 (72.8)
Negative	132 (27.2)
Level V	
Positive	101 (20.8)
Negative	385 (79.2)
Level II-ENE	
Positive	26 (5.3)
Negative	460 (94.7)
Level III-ENE	
Positive	32 (6.6)
Negative	454 (93.4)
Level IV-ENE	
Positive	44 (9.1)
Negative	442 (90.9)
Level V-ENE	
Positive	9 (1.9)
Negative	477 (98.1)
CLNM-ENE	
Positive	52 (10.7)
Negative	434 (89.3)
T stage	
T1	269 (55.3)
T2	56 (11.5)
T3	135 (27.8)
T4	26 (5.3)

Data are presented as n (%) or mean ± standard deviation. HT, Hashimoto's thyroiditis; NG, nodular goiter; ETE, extrathyroidal extension; CLNM, central lymph node metastasis; ENE, extranodal extension.

**Table 2** Binary logistic regression analysis of clinicopathological factors and lymph node metastasis at level II

Characteristics	OR	95% CI		P value
		Lower	Upper	
Tumor size >2 cm	1.632	0.806	3.301	0.17
Total tumor size >2 cm	1.097	0.597	2.018	0.77
Upper location	3.067	2.075	4.534	<0.001
Multifocality	1.422	0.902	2.242	0.13
CLNM	1.573	0.978	2.531	0.06
Level V	1.421	0.878	2.300	0.15
CLNM-ENE	2.036	1.044	3.970	0.04
Level III-ENE	1.619	0.703	3.728	0.26

OR, odds ratio; CI, confidence interval; CLNM, central lymph node metastasis; ENE, extranodal extension.

**Table 3** Binary logistic regression analysis of clinicopathological factors and lymph node metastasis at level III

Characteristics	OR	95% CI		P value
		Lower	Upper	
Upper location	2.106	1.404	3.159	<0.001
CLNM	2.664	1.681	4.222	<0.001

OR, odds ratio; CI, confidence interval; CLNM, central lymph node metastasis.

**Table 4** Binary logistic regression analysis of clinicopathological factors and lymph node metastasis at level V

Characteristics	OR	95% CI		P value
		Lower	Upper	
Male	1.256	0.787	2.007	0.34
Tumor size >2 cm	1.442	0.825	2.519	0.20
Gross ETE	1.582	0.618	4.052	0.34
Level II	1.548	0.973	2.461	0.07
CLNM-ENE	1.825	0.943	3.531	0.07
Level III-ENE	2.347	1.065	5.176	0.03
T3–4	1.361	0.826	2.244	0.23

OR, odds ratio; CI, confidence interval; ETE, extrathyroidal extension; CLNM, central lymph node metastasis; ENE, extranodal extension.

Among the patients, 381 (78.4%) had CLNM, while 105 (21.6%) did not exhibit CLNM, classified as skip metastasis. In these 105 patients, the number of cases with metastasis in levels II–V were 42, 56, 67, and 15, respectively. Three patients had gross ETE, and 63 patients had tumors located in the upper portion of the thyroid lobe. In the lateral cervical area, LNM was found at level II in 241 patients (49.6%); level III, 333 patients (68.5%); level IV, 354 patients (72.8%); and level V, 101 patients (20.8%). As for ENE, 52 cases (10.7%) exhibited ENE in the central lymph nodes (CLNs). In the lateral cervical area, II-ENE was found in 26 patients (5.3%), III-ENE in 32 patients (6.6%), IV-ENE in 44 patients (9.1%), and V-ENE in 9 patients (1.9%). The numbers of patients with T1, T2, T3, and T4 stages were 269, 56, 135, and 26, respectively, accounting for 55.3%, 11.5%, 27.8%, and 5.3% of the total number of patients. Since all the enrolled patients had lateral neck LNM, they were classified as N1b stage. Three patients developed distant metastases postoperatively.

#### *Predictive factors for metastasis at different lateral levels in N1b PTC patients*

Correlation analysis, as shown in [Tables S1–S4](#), revealed that tumor size, total tumor size, upper location, multifocality, CLNM, level V (+), CLNM-ENE, and level III-ENE were associated with LNM at level II. For LNM at level III, both upper location and CLNM were found to be closely associated. LNM at level IV was closely associated only with CLNM. Level V metastasis occurred much more frequently with the following factors: male gender, tumor size >2 cm, gross ETE, T3–4, level II (+), CLNM-ENE, and level III-ENE.

Binary logistic regression analysis, as shown in [Table 2](#), indicated that upper location (OR =3.067; P<0.001; 95% CI: 2.075–4.534) and CLNM-ENE (OR =2.036; P=0.04; 95% CI: 1.044–3.970) are predictive factors for level II metastasis. Additionally, upper location (OR =2.106; P<0.001; 95% CI: 1.404–3.159) and CLNM (OR =2.664; P<0.001; 95% CI: 1.681–4.222) were found to be predictive factors for level III metastasis ([Table 3](#)). As for level IV metastasis, since it was only associated with CLNM in the correlation analysis, binary logistic regression analysis was not further conducted. Level III-ENE (OR =2.347; P=0.03; 95% CI: 1.065–5.176) was found to be highly correlated with level V metastasis ([Table 4](#)).

**Table 5** Binary logistic regression analysis of clinicopathological factors and level II-ENE

Characteristics	OR	95% CI		P value
		Lower	Upper	
Male	1.283	0.512	3.213	0.60
Total tumor size >2 cm	1.897	0.721	4.897	0.20
Multifocality	1.738	0.661	4.565	0.26
CLNM-ENE	3.341	1.229	9.086	0.02
Level III-ENE	5.243	1.643	16.735	0.005
Level V-ENE	2.486	0.446	13.856	0.30

ENE, extranodal extension; OR, odds ratio; CI, confidence interval; CLNM, central lymph node metastasis.

**Table 6** Binary logistic regression analysis of clinicopathological factors and level III-ENE

Characteristics	OR	95% CI		P value
		Lower	Upper	
Male	1.988	0.788	5.018	0.15
Coexistent HT	0.456	0.139	1.493	0.19
Level II	1.029	0.387	2.733	0.96
Level V	2.254	0.844	6.020	0.11
CLNM-ENE	1.506	0.539	4.208	0.43
Level II-ENE	6.739	2.031	22.366	0.002
Level IV-ENE	12.370	4.946	30.936	<0.001
Level V-ENE	2.979	0.499	17.793	0.23

ENE, extranodal extension; OR, odds ratio; CI, confidence interval; HT, Hashimoto's thyroiditis; CLNM, central lymph node metastasis.

### Predictive factors for ENE at different lateral levels in N1b PTC patients

Correlation analysis presented in [Table S5](#) revealed that male gender, total tumor size (>2 cm), multifocality, CLNM-ENE, level III-ENE, level IV-ENE, and level V-ENE were associated with ENE at level II. As for ENE at level III, male sex, coexistent HT, level II (+), level V (+), CLNM-ENE, level II-ENE, level IV-ENE, and level V-ENE were found to be closely associated ([Table S6](#)). Additionally, male sex, gross ETE, CLNM-ENE, level II-ENE, level III-ENE, and level V-ENE were found to be closely associated with level IV-ENE in the correlation analysis ([Table S7](#)). Level V-ENE was found to be more

**Table 7** Binary logistic regression analysis of clinicopathological factors and level IV-ENE

Characteristics	OR	95% CI		P value
		Lower	Upper	
Male	1.100	0.522	2.320	0.80
Gross ETE	3.353	1.056	10.646	0.04
CLNM-ENE	4.293	1.861	9.900	<0.001
Level II-ENE	2.719	0.914	8.092	0.07
Level III-ENE	12.323	4.878	31.131	<0.001
Level V-ENE	0.947	0.153	5.852	0.95

ENE, extranodal extension; OR, odds ratio; CI, confidence interval; ETE, extrathyroidal extension; CLNM, central lymph node metastasis.

likely associated with tumor size >2 cm, total tumor size >2 cm, gross ETE, CLNM-ENE, level II-ENE, level III-ENE, and level IV-ENE ([Table S8](#)).

The binary logistic regression analysis, as shown in [Table 5](#), indicated that only CLNM-ENE (OR =3.341; P=0.02; 95% CI: 1.229–9.086) and level III-ENE (OR =5.243; P=0.005; 95% CI: 1.643–16.735) are predictive factors for level II-ENE. As for level III-ENE, level II-ENE (OR =6.739; P=0.002; 95% CI: 2.031–22.366) and level IV-ENE (OR =12.370; P <0.001; 95% CI: 4.946–30.936) were still identified as predictive risk factors in the binary logistic regression analysis ([Table 6](#)). Additionally, gross ETE (OR =3.353; P=0.04; 95% CI: 1.056–10.646), CLNM-ENE (OR =4.293; P<0.001; 95% CI: 1.861–9.900) and level III-ENE (OR =12.323; P<0.001; 95% CI: 4.878–31.131) were found to be closely associated with level IV-ENE ([Table 7](#)). For ENE at level V, level III-ENE (OR =8.291; P=0.04; 95% CI: 1.119–61.407) significantly increased the associated risk ([Table 8](#)).

### Discussion

In this study focusing on LLNM and ENE in various lateral neck regions of N1b PTC patients, we found that an upper location and ENE of CLNs are risk factors for level II LNM. For level III lymph nodes, an upper location and CLNM significantly increase the risk of involvement. Level IV LNM is closely associated with CLNM alone. A higher T stage (T3–4) increases the likelihood of level V LNM, and the risk of level V LNM significantly increases if ENE is present in level III lymph nodes. Additionally, ENE of

**Table 8** Binary logistic regression analysis of clinicopathological factors and level V-ENE

Characteristics	OR	95% CI		P value
		Lower	Upper	
Tumor size >2 cm	2.899	0.423	19.859	0.28
Total tumor size >2 cm	2.529	0.298	21.464	0.40
Gross ETE	2.786	0.412	18.858	0.29
CLNM-ENE	2.284	0.404	12.917	0.35
Level II-ENE	2.745	0.404	18.634	0.30
Level III-ENE	8.291	1.119	61.407	0.04
Level IV-ENE	0.708	0.079	6.311	0.76

ENE, extranodal extension; OR, odds ratio; CI, confidence interval; ETE, extrathyroidal extension; CLNM, central lymph node metastasis.

level III lymph nodes significantly increases the risk of ENE in all other lymph node levels, highlighting the central hub role of level III lymph nodes in the lateral neck. When ENE occurs in the CLNs, the risk of ENE in levels II and IV significantly increases.

In PTC patients, regional LNM is quite common, with an incidence ranging from approximately 50% to 80%, according to previous reports (15-17). Although PTC patients typically have a favorable prognosis, LNM is linked to reduced DFS and even an increased mortality rate (18,19). In our study, the risks of LNM at levels II, III, IV, and V were 49.6%, 68.5%, 72.8%, and 20.8%, respectively, with the highest risks observed in levels III and IV, consistent with previous research findings (17,20,21). The risk of level V LNM was the lowest at 20.8%, which aligns with the range reported in current literature, specifically between 8% and 25.3% (4,22,23). The nearly 50% probability of level II LNM in N1b patients in our study clearly highlights its significance in lateral neck metastasis. Recently, there has been discussion about the benefits of selective or super-selective dissection, considering that the risk of PTC metastasis to levels II and V is relatively low. Clearing lymph nodes in these areas may increase the risk of surgical complications for patients. Compared to levels III/IV, the likelihood of metastasis in levels II/V is lower, while the risk associated with extensive dissection may be significantly higher. The benefit-risk ratio of extensive dissection needs further clarification. Our study aims to analyze the characteristics and risk factors of LNM in different lateral neck levels, preliminarily mapping the metastasis patterns

and pathways in PTC patients. When significant risk factors are present, such as ENE of CLNs and involvement of pivotal level III lymph nodes, the likelihood of LNM in more distant or multiple lateral cervical regions increases, even if preoperative US does not clearly indicate LNM in these areas. At this point, careful evaluation and selection of an appropriate neck dissection method are necessary.

In this study, nearly half of the N1b PTC patients had tumors located in the upper portion of the thyroid (49.2%), which is significantly higher than those with tumors in the middle portion (32.9%) and lower portion (17.9%). This suggests that tumors located in the upper portion of the thyroid are more likely to exhibit LLNM. This finding aligns with previous research, which concluded that thyroid cancer metastasis to the lateral cervical lymph nodes is highly correlated with the occurrence of tumors in the upper portion of the thyroid (19). Likhterov *et al.* reported that tumors located in the upper portion may have an exclusive drainage pathway to the LLN regions, indicating that LND should be evaluated more meticulously for these patients (13). Furthermore, our study revealed that 21.6% of patients presented with metastasis at the lateral neck lymph nodes without involvement of the central level lymph nodes. Skip metastasis, where tumor cells bypass the CLNs and initially spread to the LLNs, has been documented in multiple studies, affecting around 21.8–23.5% of patients (24-26). This could be attributed to PTC metastasizing to the lateral neck lymph nodes through lymphatic flow along the superior thyroid artery instead of via the conventional lymphatic drainage routes (25,27). In fact, among 105 patients with skip metastasis, tumors in 63 patients were located in the upper portion of the thyroid gland (60.0%) in our study. Therefore, patients with tumors located in the upper portion of the thyroid not only have a higher risk of LLNM but also exhibit more insidious tumor behavior, bypassing the classic central compartment metastasis and directly spreading to the lateral cervical lymph nodes.

ENE is widely acknowledged as a major risk factor for the recurrence and cancer-related mortality of PTC (28). Therefore, it is essential to evaluate ENE in N1b PTC patients. In our study, the overall rates of patients with ENE in the central zone, as well as zones II, III, IV, and V lymph nodes, are 10.7%, 5.3%, 6.6%, 9.1% and 1.9%, respectively. Our study found that CLNM is closely associated with metastasis at level III and level IV lymph nodes. This correlation aligns with the anatomical proximity of these regions. A previous study has also confirmed that whether LLNM occurs along the anterior or posterior aspect of the

carotid sheath, the peritracheal lymph nodes are almost always involved (13). It indicates that when tumors involve the peritracheal lymph nodes, lymphatic drainage further directs metastasis to level III and level IV lymph nodes. Additionally, among the 329 patients in this study who had CLNM positivity without CLNM-ENE, 49.8% and 20.4% patients had level II and level V LNM, respectively. In contrast, among the 52 patients with CLNM positivity and CLNM-ENE, the numbers of patients with level II and level V LNM were 35 (67.3%) and 19 (36.5%), respectively. This suggests that the progression from CLNM to CLNM-ENE significantly raises the possibility of metastasis to more distant lymph node regions, illustrating the potential sequential pathway of LNM.

The level III lymph node region is anatomically positioned as a central hub in the lateral neck, bordered anteriorly by the CLNs, posteriorly by the V lymph nodes, superiorly by the II lymph nodes, and inferiorly by the IV lymph nodes. We propose its pivotal anatomical role in the lateral neck of thyroid cancer patients. Involvement of the III lymph nodes, particularly with ENE, increases the risk of metastasis to the level V lymph nodes. It also significantly elevates the likelihood of ENE in other regions of the lateral neck. This suggests that when the level III lymph nodes are involved in ENE, it may disrupt the conventional lymphatic drainage pathways of the lateral neck, leading to radiation of multiple surrounding lymph node areas and significantly increasing the risk of LNM spreading. Analysis of risk factors of ENE in level III lymph nodes itself indicates that extra nodal extension in level II, IV, and V lymph nodes all raise the risk of ENE in level III lymph nodes. This further confirms the pivotal central position of the level III lymph nodes in the lateral neck, which not only facilitates invasion of other lymph node regions but also makes it susceptible to metastasis from other lymph nodes in the lateral neck.

Therefore, for patients with PTC, the pathways for tumor metastasis to cervical lymph nodes are not singular. Commonly, metastasis occurs sequentially along the conventional drainage pathways of central compartment lymph nodes, followed by level III/IV lymph nodes, and further to level II/V lymph nodes (10). However, in our study, we also found that 28 patients had level II LNM without level III and IV LNM, accounting for 11.6% of the total number of patients with level II LNM. Among these 28 patients, 19 patients (67.9%) had tumors located at the upper pole of the thyroid. Meanwhile, among the 101 patients with level V LNM, 12 patients (11.9%) did

not have level III and IV LNM. Hence, LLNM in PTC exhibits a considerable degree of unpredictability and randomness. Nonetheless, amidst the uncertainties, we still aim to identify some potential patterns. When the tumor is located at the upper pole of the thyroid, the risk of lateral cervical metastasis increases, and there is a higher likelihood of skipping the central compartment, level III and level IV lymph nodes, resulting in metastasis to the more distant yet anatomically adjacent level II lymph nodes. When level III lateral cervical lymph nodes show ENE, this pivotal lymph node region may spread the tumor to surrounding areas, leading to involvement of multiple regions.

This study has some limitations. We did not analyze the incidence of sublevel metastasis (IIa/IIIb and Va/Vb) because sublevels of the specimens were not routinely labeled, so as to maintain continuity of patients. Additionally, lymphovascular invasion, more detailed characteristics of metastatic lymph nodes, BRAF mutation, and other variables might be incorporated into future predictive models. Third, the retrospective nature of our study means that nonrandomized features are inevitably produced. Therefore, future research should aim for more reliable multicentric studies with large sample sizes, employing prospective and randomized controlled designs to validate our conclusions.

## Conclusions

Our research indicates that an upper location predicts level II and III metastasis. Also, CLNM-ENE heightens the risk of level II metastasis and the occurrence of level II-ENE and level IV-ENE. Gross ETE notably increases the likelihood of level IV-ENE. Furthermore, level III acts as a hub in the lateral neck, with level III-ENE elevating the risk of level V metastasis and ENE in other regions. Additionally, ENE in other regions raises the risk of level III-ENE. LLNM have its inherent patterns, as evidenced in the study, but also have a degree of unpredictability, therefore an accurate preoperative assessment is essential.

## Acknowledgments

*Funding:* None.

## Footnote

*Reporting Checklist:* The authors have completed the STROBE reporting checklist. Available at <https://gs.amegroups.com/>

[article/view/10.21037/gs-24-299/rc](https://doi.org/10.21037/gs-24-299/rc)

*Data Sharing Statement:* Available at <https://gs.amegroups.com/article/view/10.21037/gs-24-299/dss>

*Peer Review File:* Available at <https://gs.amegroups.com/article/view/10.21037/gs-24-299/prf>

*Conflicts of Interest:* All authors have completed the ICMJE uniform disclosure form (available at <https://gs.amegroups.com/article/view/10.21037/gs-24-299/coif>). The authors have no conflicts of interest to declare.

*Ethical Statement:* The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was approved by the Ethics Committee of FUSCC (No. 050432-4-2307E) and informed consent was obtained from all participants. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

*Open Access Statement:* This is an Open Access article distributed in accordance with the Creative Commons Attribution-NonCommercial-NoDerivs 4.0 International License (CC BY-NC-ND 4.0), which permits the non-commercial replication and distribution of the article with the strict proviso that no changes or edits are made and the original work is properly cited (including links to both the formal publication through the relevant DOI and the license). See: <https://creativecommons.org/licenses/by-nc-nd/4.0/>.

## References

- Cai H, Zhuge L, Huang Z, et al. Distinct risk factors of lateral lymph node metastasis in patients with papillary thyroid cancer based on age stratification. *BMC Surg* 2024;24:24.
- Kang JG, Choi JE, Kang SH. Risk factors for level V metastasis in patients with N1b papillary thyroid cancer. *World J Surg Oncol* 2022;20:327.
- Gao L, Li X, Liu C, et al. What Are the Characteristics of Papillary Thyroid Microcarcinoma Prone to High-Volume Lateral Lymph Node Metastasis? - An Analysis of 2981 Consecutive Cases. *J Invest Surg* 2022;35:1519-25.
- Wang Y, Guan Q, Xiang J. Nomogram for predicting level V lymph node metastases in papillary thyroid carcinoma with clinically lateral lymph node metastases: A large retrospective cohort study of 1037 patients from FDUSCC. *J Cancer* 2019;10:772-8.
- Gao L, Li X, Xia Y, et al. Large-Volume Lateral Lymph Node Metastasis Predicts Worse Prognosis in Papillary Thyroid Carcinoma Patients With N1b. *Front Endocrinol (Lausanne)* 2021;12:815207.
- Farias T, Kowalski LP, Dias F, et al. Guidelines from the Brazilian society of surgical oncology regarding indications and technical aspects of neck dissection in papillary, follicular, and medullary thyroid cancers. *Arch Endocrinol Metab* 2023;67:e000607.
- Uludağ M, Tanal M, İlgör A. Standards and Definitions in Neck Dissections of Differentiated Thyroid Cancer. *Sisli Etfal Hastan Tip Bul* 2018;52:149-63.
- Haugen BR, Alexander EK, Bible KC, et al. 2015 American Thyroid Association Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer: The American Thyroid Association Guidelines Task Force on Thyroid Nodules and Differentiated Thyroid Cancer. *Thyroid* 2016;26:1-133.
- Ngo DQ, Le DT, Ngo QX, et al. Modified Radical Neck Dissection for Papillary Thyroid Carcinoma via a Combined Endoscopy Approach: The Transoral Approach and the Chest Approach. *Ann Surg Oncol* 2024;31:2357-8.
- Kim SK, Park I, Hur N, et al. Should Level V Be Routinely Dissected in N1b Papillary Thyroid Carcinoma? *Thyroid* 2017;27:253-60.
- Caron NR, Tan YY, Ogilvie JB, et al. Selective modified radical neck dissection for papillary thyroid cancer-is level I, II and V dissection always necessary? *World J Surg* 2006;30:833-40.
- Dou Y, Hu D, Chen Y, et al. PTC located in the upper pole is more prone to lateral lymph node metastasis and skip metastasis. *World J Surg Oncol* 2020;18:188.
- Likhterov I, Reis LL, Urken ML. Central compartment management in patients with papillary thyroid cancer presenting with metastatic disease to the lateral neck: Anatomic pathways of lymphatic spread. *Head Neck* 2017;39:853-9.
- Yang Z, Heng Y, Zhao Q, et al. A Specific Predicting Model for Screening Skip Metastasis From Patients With Negative Central Lymph Nodes Metastasis in Papillary Thyroid Cancer. *Front Endocrinol (Lausanne)* 2021;12:743900.
- Lim J, Lee HS, Heo JH, et al. Clinicopathological Features and Molecular Signatures of Lateral Neck Lymph Node Metastasis in Papillary Thyroid Microcarcinoma. *Endocrinol Metab (Seoul)* 2024;39:324-33.

16. Yuan Y, Pan B, Mo H, et al. Deep learning-based computer-aided diagnosis system for the automatic detection and classification of lateral cervical lymph nodes on original ultrasound images of papillary thyroid carcinoma: a prospective diagnostic study. *Endocrine* 2024;85:1289-99.
17. Eskander A, Merdad M, Freeman JL, et al. Pattern of spread to the lateral neck in metastatic well-differentiated thyroid cancer: a systematic review and meta-analysis. *Thyroid* 2013;23:583-92.
18. Ruan J, Chen Z, Chen S, et al. Lateral lymph node metastasis in papillary thyroid microcarcinoma: a study of 5241 follow-up patients. *Endocrine* 2024;83:414-21.
19. Heng Y, Feng S, Yang Z, et al. Features of Lymph Node Metastasis and Structural Recurrence in Papillary Thyroid Carcinoma Located in the Upper Portion of the Thyroid: A Retrospective Cohort Study. *Front Endocrinol (Lausanne)* 2021;12:793997.
20. Yanir Y, Doweck I. Regional metastases in well-differentiated thyroid carcinoma: pattern of spread. *Laryngoscope* 2008;118:433-6.
21. Kim SK, Park I, Hur N, et al. Patterns, predictive factors and prognostic impact of multilevel metastasis in N1b papillary thyroid carcinoma. *Br J Surg* 2017;104:857-67.
22. Song K, Jin Y, Kim M, et al. Patterns of Occult Metastasis to Level Va and Vb in Clinically Lateral Node-Positive Papillary Thyroid Carcinoma. *Ann Surg Oncol* 2022;29:2550-6.
23. Lombardi D, Taboni S, Paderno A, et al. Lateral neck dissection for aggressive variants of well-differentiated thyroid cancer. *Endocr Pract* 2019;25:328-34.
24. Liu WQ, Yang JY, Wang XH, et al. Analysis of factors influencing cervical lymph node metastasis of papillary thyroid carcinoma at each lateral level. *BMC Surg* 2022;22:228.
25. Feng JW, Qin AC, Ye J, et al. Predictive Factors for Lateral Lymph Node Metastasis and Skip Metastasis in Papillary Thyroid Carcinoma. *Endocr Pathol* 2020;31:67-76.
26. Zhao Y, Li W, Tao L, et al. Risk factors and nomogram to predict skip metastasis in papillary thyroid carcinoma. *Gland Surg* 2024;13:178-88.
27. Lee YS, Shin SC, Lim YS, et al. Tumor location-dependent skip lateral cervical lymph node metastasis in papillary thyroid cancer. *Head Neck* 2014;36:887-91.
28. Limberg J, Lee-Saxton YJ, Egan CE, et al. Perineural Invasion in Papillary Thyroid Cancer: A Rare Indicator of Aggressive Disease. *Ann Surg Oncol* 2023;30:3570-7.

**Cite this article as:** Zhang Y, Ji X, Zhang X, Wang Y. Risk factors for cervical lymph node metastasis at different lateral levels in papillary thyroid cancer: level III as the central hub. *Gland Surg* 2024;13(11):1921-1930. doi: 10.21037/gs-24-299