Prediction of lateral neck metastasis in patients with papillary thyroid cancer with suspicious lateral lymph ultrasonic imaging based on central lymph node metastasis features

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Received November 21, 2023; Accepted July 12, 2024

DOI: 10.3892/ol.2024.14605

Abstract. Neck lymphatic metastasis is a common occurrence with thyroid cancers, and pre operative lateral lymph node metastasis (LLNM) and postoperative lateral lymph node recurrence (LLNR) are two independent risk factors that are negatively associated with the prognosis of patients with thyroid cancer. The aim of the present study was to investigate the relationship between central lymph node metastasis (CLNM) and LLNM in patients with papillary thyroid carcinoma (PTC) with sonographically suspected LLNM, such as those without lymph node fine-needle aspiration (FNA) cytological results or negative FNA results at the time of diagnosis. The predictive ability of CLNM regarding LLNR was also investigated. The present study retrospectively reviewed the clinical data of 1,061 patients that were surgically treated for PTC and 128 patients with sonographically suspected lateral lymph nodes that received central lymph node dissection and lateral lymph node dissection at the Thyroid Department of The First Affiliated Hospital of Anhui Medical University (Hefei, China) from June 2019 to June 2021. In patients with suspicious ultrasonic images suggesting LLNM, a significant association between the central lymph node ratio (CLNR), the number of positive central lymph nodes and LLNM was demonstrated. Otherwise, there were no statistically significant differences between the CLNR in patients with PTC and patients with PTC without evidence of lateral cervical metastasis. However, the rate of LLNR increased significantly when the number of positive central lymph nodes was >3. In conclusion, the CLNR and the number of positive central lymph nodes could be used to predict LLNM in patients with PTC with sonographically suspect lateral lymph nodes, including those with no FNA cytological results or negative FNA results, which may potentially support physicians in making personalized clinical decisions.

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Key words: lateral lymph node metastasis, number of positive central lymph nodes, central lymph node ratio, lateral neck lymph node recurrence

Introduction

Due to the increased use of physical examinations and the wider application of high-resolution ultrasound and enhanced CT, the availability of accurate early diagnostic techniques for thyroid carcinoma has notably increased in all malignant tumors. Papillary thyroid carcinoma (PTC) accounts for >90% of all malignant thyroid tumors and is usually considered a low-grade malignant tumor with good prognosis (1-3). Recent cancer statistics, indicate that the 5-year relative survival rate for thyroid cancer is ~99% (3). Cervical lymph node metastases are common in patients with PTC, occurring in 30-80% of cases (4). PTC often manifests in the central (compartments VI) and lateral neck (compartments II-V) lymph nodes, with the central lymph node generally considered to be the first site of PTC, with a high rate of metastasis (5). Central lymph node dissection (CLND) does not require a longer incision and has no difference in the probability of recurrent laryngeal nerve injury compared with those who don't undergo CLND, therefore, CLND is routinely performed to treat PTC (5,6). However, lateral lymph node dissection (LLND) in patients with PTC is controversial, especially for patients without evidence of lateral cervical metastasis (cN1b-). Furthermore, the 2015 American Thyroid Association (ATA) guidelines state that prophylactic lateral neck dissection is not recommended in patients with PTC without clinically involved lateral compartment lymph nodes (cN1b+) (7). However, even after appropriate treatment, 10-20% of patients that are cN1b- experience lateral lymph node recurrence (LLNR) and require re-operation during follow-up (8). Furthermore, there are certain patients with suspicious ultrasound images including loss of the fatty hilum, a rounded rather than oval shape, cystic change, calcifications and peripheral vascularity, of the lateral lymph node metastasis (LLNM) but without preoperative fine-needle aspiration (FNA) cytological results or negative FNA results; whether to perform LLND in these cases is considered to be controversial (5).

In the present retrospective study, the association between central lymph node metastasis (CLNM) and LLNM in patients with sonographically suspicious lateral lymph nodes, as well as the incidence of LLNR in postoperative patients that were classed as cN1b- were investigated. The aim of the present study was to provide a basis for the selection of clinical treatment strategies in these patients.

Materials and methods

Study patients. The present study reviewed patients with PTC who underwent surgery from June 2019 to June 2021 at the Thyroid Department of The First Affiliated Hospital of Anhui Medical University (Hefei, China). The exclusion criteria included: i) Inadequate medical records; ii) distant metastases; iii) a history of treatments for other types of cancer; and iv) follow-up data of <2 years. A total of 1,061 patients were included in the present study and 128 of these patients had preoperative ultrasonic imaging examination results that were indicative of LLNM (9). Patient characteristics and cervical lymph node clinicopathologic features were carefully reviewed. The numbers of metastatic and central lymph node yield, the central lymph node ratio (CLNR; the number of positive central lymph nodes divided by the number of central lymph node yield) and CLNM were identified using postoperative pathological reports. All patients were pathologically confirmed to have PTC through pathologic examination. The present study was approved by the Ethics Committee of the First Affiliated Hospital of Anhui Medical University (Hefei, China).

Treatments and follow-up. All patients included in the study were examined by preoperative high-resolution ultrasonography at the ultrasound department of The First Affiliated Hospital of Anhui Medical University (Hefei, China), according to the European Thyroid Association guidelines definition of ultrasonography-detectable LLNM (9).

Hemi-thyroidectomy, isthmus and ipsilateral CLND was routinely performed for unilateral PTC, and total thyroidectomy and bilateral CLND were performed for bilateral PTC, regardless of central lymph node involvement (as per the Chinese Thyroid Association guidelines) (10). The central lymph node is bordered superiorly by the hyoid bone, laterally by the carotid sheaths and inferiorly by the innominate (brachiocephalic) artery and is closely associated with the prelaryngeal lymph nodes, pretracheal lymph nodes and the paratracheal lymph nodes. Patients that were suspected to have LLNM underwent primary thyroid tumor resection, and central region VI and lateral cervical selective lymph node dissection (region II-V) (11,12).

All 1,061 patients were treated with thyroid stimulating hormone suppressive therapy after surgery (12). Postoperative radioiodine treatment was administered to patients who had intermediate or high-risk stratification for recurrence according to intraoperative and pathologic findings (7).

Patients were followed up every 3 months during the first year and then every 6 months thereafter. Clinical examinations, thyroid function tests, thyroid and cervical lymph node ultrasonography and chest radiography were used to assess the condition of the patients. LLNR was defined as the first occurrence of positive lymph nodes in the lateral cervical region during the follow-up period after the initial standard operation and was diagnosed using ultrasound-guided FNA cytology.

Statistical analysis. χ^2 tests and Fisher's exact tests were used as appropriate to identify single risk factors for LLNM. Logistic regression analysis was used to calculate the odds ratios (ORs) of certain parameters. Results were presented as ORs with 95% confidence intervals (CI) and P-values. Receiver operating characteristic (ROC) curve analysis was performed to determine the cut-off number of positive central lymph nodes. P<0.05 was considered to indicate a statistically significant difference. Statistical analysis was performed using SPSS (version 26; IBM Corp.).

Results

Patient characteristics. A total of 1,061 patients were included in the present study (Table I). Of these patients, 128 were individuals with sonographically suspicious LLNM that received both central and LLND. Among these, 94 (73.4%) patients were diagnosed with CLNM and 106 (82%) with lymph node metastasis in both the central and lateral compartments using postoperative pathology examination. The mean number of metastatic lymph nodes in the central compartment was 3.68±3.05, the mean number of central lymph node yield was 6.25±3.37 and the CLNR was 0.57±0.37. A total of 933 patients without LLNM (cN1b-) were included in the present study, and underwent CLND directly after the discovery of the lesion. There were 503 (53.9%) cases of pathologic central lymph node metastases. The mean number of metastatic lymph nodes in the central neck was 1.11±1.44, the mean number of central lymph node yield was 5.14±2.59 and the CLNR was 0.16±0.23.

During a median follow-up period of 32 months (range, 25-50 months), 31 of the patients were diagnosed with lateral cervical lymph node recurrence and underwent modified radical LLND. A total of 12 male patients and 19 female patients had lateral neck recurrence, and among these, 26 (83.9%) were <55 years of age. The pathological data relating to the primary surgery in these recurrent patients were reviewed, and the overall rate of CLNM was 25/31 patients (80.6%) in the first surgery. The mean number of metastatic lymph nodes in the central compartment was 3.48±2.94, the mean number of central lymph node yield was 6.58±3.68 and the CLNR was 0.52±0.37.

Association between CLNM and lateral neck lymph node metastasis. The association between CLNM and lateral neck lymph node metastasis was investigated and the difference was statistically significant (P<0.001). Patients with suspicious LLNM had a significantly higher incidence of positive central lymph nodes [84 (79.2%) vs. 10 (45.5%), P=0.001; Table II].

Univariate analysis showed that the CLNR and the number of positive central lymph nodes was significantly associated with LLNM (P<0.05). Multivariate analysis showed that the CLNR (OR=8.538, P=0.016) and the number of positive central lymph nodes (OR=2.234, P=0.023) were significant independent risk factors for LLNM (Table III).

Table I. Characteristics of included patients with PTC (n=1,061).

Characteristic	CLND + LLND	CLND	LLN recurrence
No. of patients	128	933	31
Patient sex, n (%)			
Male	36 (28.1)	260 (27.9)	12 (38.7)
Female	92 (71.9)	673 (72.1)	19 (61.3)
Age, n (%)			
<55 years	81 (63.3)	654 (70.1)	26 (83.9)
≥55 years	47 (36.7)	279 (29.9)	5 (26.1)
CLNM, n (%)	94 (73.4)	503 (53.9)	25 (80.6)
LLNM, n (%)	106 (82.0)	-	-
LLN recurrence, n (%)	-	31 (3.4)	-
No. of metastatic lymph nodes in central neck, mean (SD)	3.68 (3.05)	1.11 (1.44)	3.48 (2.94)
Central lymph node yield, mean (SD)	6.25 (3.37)	5.14 (2.59)	6.58 (3.68)
Lymph node ratio in central neck, mean (SD)	0.57 (0.37)	0.16 (0.23)	0.52 (0.37)
Follow-up time in months, median (range)	32 (25-50)	32 (25-50)	25 (18-36)

-, Not applicable; LLN, lateral lymph node; LLND, lateral lymph node dissection; CLND, central lymph node dissection; LLNM, lateral lymph node metastasis; CLNM, central lymph node metastasis.

Table II. Relationship between CLN ratio and LLNM in patients with PTC (n=128).

CLN status	LLNM-positive, (n=106)	LLNM-negative, (n=22)	P-value
Positive, n (%)	84 (79.2)	10 (45.5)	0.001
Negative, n (%)	22 (21.8)	12 (54.5)	

CLN, central lymph node; LLNM, lateral lymph node metastasis.

Table III. Univariate and multivariate analysis of CLNR, number of positive central lymph node and lateral lymph node metastasis.

	Univariate		Multivariate	
Characteristic	OR (95% CI)	P-value	OR (95% CI)	P-value
CLNR	13.035 (3.018-66.053)	<0.001	8.538 (1.547-53.411)	0.016
No. of positive central lymph nodes	2.554 (1.188-18.031)	0.001	2.234 (0.732-9.138)	0.023

OR, odds ratio; CLNR, central lymph node ratio.

The association between LLNM and the number of positive central lymph nodes was further analyzed (Table IV). The 128 patients were divided into groups according to the number of positive central lymph nodes. The rate of LLNM notably increased with the number of positive central lymph nodes as follows: 9.1% in patients with one positive central lymph node, 63.6% in patients with two positive central lymph nodes and 80-100% in patients with ≥3 positive central lymph nodes.

The optimal cut-off number of positive central lymph nodes to differentiate patients with or without LLNM was 3, which was used to divide the patients into three groups (Fig. 1). The groups included: i) Group A, no positive

Table IV. Patients with LLNM grouped according to the number of positive central lymph nodes.

	No. of positive central lymph nodes							
Parameter	0	1	2	3	4	5	6	≥7
No. of patients, (n=128)	34	11	11	20	16	15	5	16
No. of patients with LLNM, (n=106)	22	9	7	18	16	14	4	16
Incidence of patients with LLNM, %	64.7	9.1	63.6	90.0	100.0	93.3	80.0	100.0

LLNM, lateral lymph node metastasis.

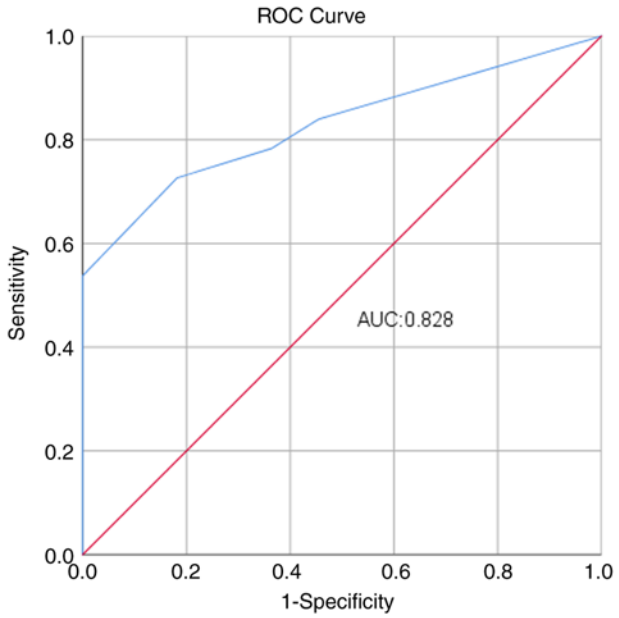

Figure 1. ROC curve analysis was performed to determine the cut-off number of positive central lymph nodes. ROC, receiver operating characteristic; AUC, area under the curve.

central lymph nodes; ii) group B, 1-2 positive central lymph nodes; and iii) group C, ≥3 positive central lymph nodes (Table V). Comparisons between the three groups were examined using the χ^2 test, and the incidence of LLNM was shown to be significantly increased in group C compared with that of groups A and B (P<0.05). There was no statistically significant difference identified between group A and group B (P=0.530).

The association between LLNM and CLNR was further examined by division of the lateral neck lymph nodes into compartments II-V, according to 2015 ATA guidelines (7). The logistic regression analysis results showed that with the increase in CLNR, the risk of lymph node metastasis involving levels III, IV and V increased (Table VI).

Association between CLNM and lateral neck lymph node recurrence. In the 933 patients that were cN1b-, the CLNR was 53.5% (398/744). A total of 31 of these patients developed secondary lateral cervical lymph node metastasis. Univariate analyses indicated that there was no association between CLNR and lateral cervical lymph node recurrence. However, the number of positive central lymph nodes was significantly associated with lateral neck recurrence. Specifically, when the number of CLNM was ≥3, the risk of lateral neck lymph node recurrence was significantly increased (P<0.05; Table VII).

Discussion

CLNM is the most common metastasis in patients with PTC and often follows a stepwise spread pattern, initially occurring in the central lymph node (level VI) and spreads to the LLN (level II-V) (13). Due to this, the association between CLNM and lateral neck lymph node metastasis has been investigated in numerous studies. Previous reports have shown that CLNM is an important independent predictive factor for LLNM (13-15).

The extent of cervical lymph node dissection is a subject of debate; specifically, whether CLND alone or LLND combined directly affects follow-up treatment, and whether it is related to the prognosis (16,17). According to the guidelines of 2015 ATA, therapeutic lateral neck compartmental lymph node dissection should be performed for patients with biopsy-proven metastatic lateral cervical lymphadenopathy (7). However, not all patients are suitable for FNA, including those with cystic lymph nodes, whose cyst fluid tends to cause cancer cells to spread. Furthermore, in certain patients with PTC, the puncture result is negative, but imaging results are indicative of LLNM.

The present study differed from previous studies as it included patients with PTC that had the lymph nodes in the lateral cervical region that were identified as suspicious metastases through cervical ultrasounds. These patients underwent CLND and LLND, regardless of the FNA results. Postoperative pathological examination confirmed that the rate of CLNM and LLNM was 73.4 and 82%, respectively. Previous studies have reported that ultrasonography and enhanced CT are specific and sensitive for the recognition of cervical lymph node metastasis (18,19). The present study aimed to find alternate methods to improve the diagnostic accuracy of lateral CLNM, besides preoperative ultrasound and CT evaluation. Therefore, the association between CCLM and LLNM was analyzed and it was found that patients with suspected LLNM had an increased incidence of positive central lymph nodes. Using univariate and multivariate analyses, it was shown that the number of positive central lymph nodes and the rate of central lymph nodes were independent risk factors for LLNM

Table V. Relationship between the number of positive CLNs and LLNM.

Parameter	Group A	Group B	Group C	P-value
No. of patients	34	22	72	
LLNM, n (%)				0.530[a]
Negative	12 (35.3)	6 (27.3)	4 (5.66)	<0.001[b]
Positive	22 (64.7)	16 (72.7)	68 (94.4)	0.004[c]

Group A had no positive CLNs, group B had 1 or 2 positive CLNs and group C had ≥3 positive CLNs. [a]P-value between Group A and Group B; [b]P-value between group A and group C; [c]P-value between group B and group C. CLN, central lymph node; LLNM, lateral lymph node metastasis.

Table VI. Univariate analysis of CLNR and different regional lateral lymph node metastases.

Lateral neck lymph node compartments	Univariate	
	OR (95% CI)	P-value
Level II	0.833 (0.312-2.943)	0.719
Level III	3.217 (1.304-8.956)	0.030
Level IV	7.124 (2.733-24.439)	<0.001
Level V	9.636 (1.258-67.759)	0.037

OR, odds ratio; CLNR, central lymph node ratio.

Table VII. Univariate and multivariate analysis of CLNR, the number of positive central lymph nodes and recurrence of lateral neck lymph node.

	Univariate		Multivariate	
Characteristic	OR (95% CI)	P-value	OR (95% CI)	P-value
CLNR	1.018 (0.968-1.030)	0.231	0.938 (0.917-1.011)	0.412
No. of positive central lymph nodes	3.521 (1.604-10.531)	0.024	2.544 (0.664-8.183)	0.043

CLNR, central lymph node ratio.

in patients with PTC. Therefore, further assessment of these factors was carried out.

Firstly, the number and incidence of LLNM were assessed in each group according to the number of positive central lymph nodes, and it was found that the incidence of LLNM increased with the number of positive central lymph nodes. Similar results were found in previous studies (20,21) including that by Wang *et al* (22) who found that differences in LLNM incidences were significant among the 0, 1-2 and ≥3 CLNM groups (16.53% vs. 41.61% vs. 64.58%; P<0.001). In the present study, when the number of positive central lymph nodes was ≥3, the accuracy of the diagnosis of LLNM reached 94.4% when in combination with the suspicious results of preoperative imaging. Notably, the model incorporating preoperative suspicious ultrasound results and the number of positive lymph nodes during surgery demonstrated increased accuracy (94.4% vs. 64.58%) in predicting CLNM, when compared with the study by Wang *et al* (22). Furthermore, the present study demonstrated that three positive central lymph nodes was the optimal cut-off number for differentiating patients with PTCs with or without LLNM using the ROC curve. Hence, the patients with PTC were divided into three groups depending on whether the number of positive central lymph nodes diagnosed. It was found that the incidence of LLNM in patients with PTC with ≥3 positive central lymph nodes was significantly increased compared with those with 1 and 2 positive central lymph nodes or with no positive central lymph nodes.

Secondly, published ATA guidelines have queried whether LLNM should include level IIb, III and IV lymph nodes in patients with clinical lateral metastases (7). The results of the present study suggested that with the increase of CLNR, the risk of lymph node metastasis in levels III, IV and V increases. Therefore, it is not recommended for patients

with PTC with increased CLNR to undergo selective lymph node dissection in level IIb, III and IV, which could potentially lead to the omission of lymph nodes in other regions. It could be suggested that due to the low metastasis rate in area Va and the difficulty of exposure (22-24), the extent of LLND should include at least level IIa, IIb, III, IV and Vb lymph nodes.

Ipsilateral lateral neck recurrence is a common mode of recurrence, which usually involves lymph node metastases (25-27). In the present study, LLNR was detected in 2.6% (31/933) of patients, which was in accordance with a previous report (28). Recent studies focus particularly on the association between CLNM and recurrence of lateral neck lymph node. Xu *et al* (29) performed a study that included ~2,500 patients who underwent thyroidectomy and unilateral central compartment dissection. They found that an increased risk of LNR was associated with >6 CLNMs and the 5-year lateral neck recurrent-free survival rate was significantly worse for patients with >3 CLNMs compared with that in patients with £3 CLNMs. Gui *et al* (30) found that recurrence was significantly increased in patients with >5 positive lymph nodes.

Kang *et al* (31) identified that LNR values ≥0.29 were an independent prognostic factor for recurrence in a retrospective study. They found that patients with an LNR value ≥0.29 had an increased risk of recurrence compared with those with a lower LNR (31). In the present study, there was no statistically significant association identified between LNR and lateral neck lymph node recurrence. This was in accordance with a study by Lee *et al* (32) which also failed to find a significant difference between LNR and recurrence-free survival in 136 patients with PTC with cN1b who underwent thyroidectomy and therapeutic central and lateral neck dissection. However, the present study found that when the number of positive lymph nodes in the central region was >3, the risk of lateral neck lymph node recurrence increased 3.5-fold. Therefore, patients with ≥3 CLNMs should be closely followed up, and early intervention should be carried out if there are imaging abnormalities of lateral neck lymph nodes.

The present study, however, had several limitations. Firstly, as a retrospective study, it was susceptible to selection bias. Secondly, the present study was conducted as a single-center retrospective analysis with certain inherent limitations. Thirdly, all the patients included in the present study were of Chinese ethnicity. Therefore, this may limit the application of the conclusions of the present study with respect to patients of other ethnicities with PTC. Future studies should include a multi-center prospective study with a larger sample size that will obtain more accurate and objective conclusions.

In conclusion, CLNM was more likely to occur in patients with PTC, and the rate and number of CLNMs was associated with LLNM. During the surgical treatment of these patients with PTC presenting with suspicious lateral lymph nodes but lack cytological results from lymph node (FNA) or have negative FNA results at the time of diagnosis, the CLNR level and number of positive central lymph nodes could be assessed through intraoperative frozen section examination, if the number of positive central lymph nodes is ≥3, it is advisable to extend the incision length in real time to search for suspicious lateral lymph nodes and assess the presence of LLNM. After confirming CLNM ≥3 in the postoperative pathological results, it is recommended to intensify postoperative observation, conduct regular follow-ups, and repeat FNA in suspicious lateral lymph nodes for patients with PTC.

Acknowledgements

Not applicable.

Funding

This work was supported by the Clinical Research Project of the First Affiliated Hospital of Anhui Medical University (grant no. LCYJ2021YB014) and the University Research Project of Anhui Province (grant no. 2022AH040161).

Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

YX and CZ designed the research scheme. YX collected data. YX and CZ wrote and revised the manuscript. YX performed the statistical analysis. CZ and YX read and approved the final manuscript. YX and CZ confirm the authenticity of all the raw data.

Ethics approval and consent to participate

The study was approved by the Ethics Committee of the First Affiliated Hospital of Anhui Medical University (Hefei, China; approval no. PJ2023-04-44) and informed patient consent was waived.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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