



Analysis of risk factors for lateral lymph node metastasis in papillary thyroid carcinoma: A retrospective cohort study

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None

Abstract

Objective: To investigate the risk factors for lateral lymph node metastasis (LLNM) in papillary thyroid carcinoma (PTC).

Methods: A retrospective analysis of 209 patients with PTC who underwent primary surgery at the Beijing Friendship Hospital affiliated with Capital Medical University from November 2014 to November 2018 was performed. The patients were divided into the LLNM group and the non-LLNM group. The clinical and pathological characteristics of the patients were analysed. The risk factors for LLNM were analysed by univariate and multivariate analyses.

Results: The incidence of LLNM was 13.4% in PTC patients. Univariate analysis showed that the maximum diameter of the primary tumour > 2 cm ($P < 0.001$), bilateral primary tumour ($P = 0.020$), extrathyroidal extension (ETE) ($P < 0.001$), central lymph node metastasis (CLNM) ($P < 0.001$), and CLNM number ≥ 5 ($P < 0.001$) were significantly associated with LLNM. Multivariate logistic regression analysis showed that the maximum diameter of the primary tumour > 2 cm, ETE, and CLNM were independent risk factors for LLNM (OR values were 3.880, 5.202, and 4.474, respectively). There were 6 patients with skip lateral cervical lymph node metastasis, accounting for 21% of all LLNM patients.

Conclusion: This study revealed several independent risk factors for predicting LLNM in PTC patients, such as the maximum diameter of the primary tumour > 2 cm, ETE and CLNM. Lateral neck dissection may be recommended in PTC patients with those risk factors. Paying attention to the occurrence of skip lateral cervical lymph node metastasis during the clinical diagnosis and treatment processes is necessary.

KEYWORDS

Cervical lymph nodes, Metastasis, Papillary thyroid carcinoma, Risk factors

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INTRODUCTION

Papillary thyroid carcinoma (PTC) is the most common malignant tumour of thyroid tumours, accounting for approximately 83.6% of all malignant tumours of the thyroid.¹ In Surveillance, Epidemiology, and End Results (SEER) and National Cancer Data Base (NCDB) cohorts, PTC patients at stage I usually have a good prognosis, with a 10-year overall survival (OS) rate greater than 95%.² However, the lymph node metastasis rate in PTC is high,³ and lymph node metastasis, particularly regarding lateral lymph node metastasis (LLNM), has a significant correlation with shorter disease-free survival.^{4–6} In the American Thyroid Association guidelines of differentiated thyroid cancer, central and/or lateral lymph node dissection is recommended when there is clinical or radiographic evidence of lymph node metastasis, while prophylactic lateral lymph node dissection is not recommended,⁷ and prophylactic central lymph node dissection remains contentious in the setting of cNO disease.^{8–10} In fact, there is still a considerable number of LLNMs and primary tumour recurrence after first surgery.¹¹ Therefore, finding the risk factors for LLNM is of great significance for clinical treatment. The purpose of this study was to analyse the risk factors for LLNM in PTC and to provide more evidence for lateral lymph node dissection indications.

MATERIALS AND METHODS

Patients and clinical data collection

A retrospective analysis of 209 PTC patients who underwent initial thyroid surgery at the Beijing Friendship Hospital Affiliated with Capital Medical University between November 2014 and November 2018 was performed. All enrolled patients received thyroid surgery for the first time and did not have other pathological types of thyroid carcinoma. This retrospective clinical research was approved by the Friendship Hospital Institutional Review Board. Electronic medical records and pathological reports were reviewed to collect clinical and pathological characteristics, including sex, age, maximum diameter of the primary tumour, primary tumour side, multifocality, extrathyroidal extension (ETE), central lymph node metastasis (CLNM), the number of CLNMs, Hashimoto's thyroiditis (HT), and the location of the primary tumour. The count data, such as the maximum diameter of the primary tumour and the number of CLNMs, were sorted into qualitative data according to a cut-off point.

Surgical indications for lateral cervical lymph node dissection

The surgical indications for lateral cervical lymph node dissection were as follows. First, preoperative cervical color Doppler ultrasound was highly suspected of LLNM, in addition, the ETE or CLNM was found during the operation. Second, the pathological results of the lateral cervical lymph node puncture were positive for metastasis. If at least

one of the above conditions is met, consider lateral cervical lymph node dissection. The final diagnosis of LLNM is subject to pathological results.

Statistical analysis

The data were analysed by SPSS 20.0 (SPSS Inc., Chicago, IL, USA). Univariate analysis was performed with the chi-squared (χ^2) test. Multivariate analysis was performed with a logistic regression model, and the likelihood ratio-based regression method was used to screen the independent variables. $P < 0.05$ was considered statistically significant.

RESULTS

The clinical and pathological characteristics of all PTC patients are shown in Table 1. Among the 209 enrolled PTC patients, 146 (69.9%) were female. The mean age was 45.51 ± 11.6 years with a range of 19–79 years. Of all the patients, 20 (9.6%) patients had a maximum diameter of the primary tumour > 2 cm, 40 (19.1%) patients had bilateral primary tumours and 72 (34.4%) patients had multifocal primary tumours. ETE was present in 76 (36.4%) patients. CLNM was seen in 89 (42.6%) patients, and CLNM numbers ≥ 5 were seen in 29 (13.9%) patients. HT was reported in 50 (23.9%) patients. All patients received the follow-up more than half a year. No lateral lymph node metastasis were observed for the patient who underwent central lymph node dissection.

Among the 209 PTC patients, LLNM was found in 28 (13.4%) patients. 5 patients were suspected of having LLNM before the operation. During the operation, lateral cervical lymph node dissection was performed, but the final pathological results showed no LLNM. All patients with LLNM received I¹³¹ treatment after surgery. However, one patient eventually developed lung metastasis, and another patient developed bone metastasis. The results of the univariate analysis of the clinicopathological characteristics between LLNM-negative and LLNM-positive patients are presented in Table 2. LLNM was significantly higher in patients with a maximum diameter of the primary tumour > 2 cm ($P < 0.001$), a bilateral primary tumour ($P = 0.020$), ETE ($P < 0.001$), CLNM ($P < 0.001$), and CLNM numbers ≥ 5 ($P < 0.001$). However, sex, age, multifocal primary tumours, and HT were not significantly associated with LLNM. In addition, as shown in Table 3, the location of the primary tumour was clearly recorded in 97 cases. There were no significant differences between LLNM-positive and LLNM-negative patients ($\chi^2 = 8.167$, $P = 0.147$).

In the multivariate logistic regression analysis, LLNM was independently correlated with tumour size > 2 cm (OR = 3.880, 95% CI = 1.278–11.779, $P = 0.017$), ETE (OR = 5.202, 95% CI = 1.993–13.580, $P = 0.001$) and CLNM (OR = 4.474, 95% CI = 1.636–12.232, $P = 0.004$) (Table 4). The Hosmer and Lemeshow Test showed $P = 0.588 > 0.2$, which means that after excluding independent variables such as sex, age, bilateral primary tumour, multifocality and HT, this regression model fit the original data better.

Skip LLNM refers to the occurrence of LLNM but without CLNM. In this retrospective cohort study, a total of 6 patients had skip

TABLE 1 Clinical and pathological characteristics of PTC patients.

Variable	n	%
Sex		
Male	63	30.1
Female	146	69.9
Age		
<55	166	79.4
≥55	43	20.6
Tumour size		
≤2 cm	189	90.4
>2 cm	20	9.6
Side		
Unilateral	169	80.9
Bilateral	40	19.1
Multifocality		
No	137	65.6
Yes	72	34.4
ETE		
No	133	63.6
Yes	76	36.4
CLNM		
No	120	57.4
Yes	89	42.6
CLNM no.		
<5	180	86.1
≥5	29	13.9
HT		
No	159	76.1
Yes	50	23.9

Abbreviations: CLNM, central lymph node metastasis; CLNM no., central lymph node metastasis number; ETE, extrathyroidal extension; HT, Hashimoto's thyroiditis.

LLNM, accounting for 2.9% of all patients enrolled in the study and 21% of LLNM patients. Among the 6 patients, all were female, 5 had capsule invasion, 5 had a single lesion, and 4 had an upper primary tumour location of the thyroid (Table 5). Skip LLNM may be related to these factors.

DISCUSSION

The indication of PTC lateral cervical lymph node dissection is one of the problems that plague clinicians. According to the 2015 American Thyroid Association Management Guidelines for Adult Patients with

TABLE 2 Univariate analysis of lateral lymph node metastasis.

Variable	OR	95% CI	P value
Sex	1.342	0.581~3.098	0.491
Age	1.343	0.530~3.403	0.535
Tumour size	5.209	2.140~12.677	<0.001
Side	2.796	1.175~6.652	0.020
Multifocality	2.121	0.949~4.738	0.067
ETE	6.873	2.760~17.111	<0.001
CLNM	6.239	2.409~16.160	<0.001
CLNM no.	8.937	3.624~22.043	<0.001
HT	1.070	0.426~2.688	0.886

Abbreviations: CLNM, central lymph node metastasis; CLNM no., central lymph node metastasis number; ETE, extrathyroidal extension; HT, Hashimoto's thyroiditis.

TABLE 3 Univariate analysis of lateral cervical lymph node metastasis and primary tumour location.

Lateral lymph node metastasis	Negative	Positive	Total
Upper	20	6	26
Middle	29	5	34
Lower	23	0	23
Dorsal	3	1	4
Nearly isthmus	6	0	6
Others	4	0	4

TABLE 4 Multivariate logistic regression analysis of lateral lymph node metastasis

Variable	OR	95% CI	P value
Tumour size > 2 cm	3.880	1.278-11.779	0.017
ETE	5.202	1.993-13.580	0.001
CLNM	4.474	1.636-12.232	0.004

Abbreviations: CLNM, central lymph node metastasis; ETE, extrathyroidal extension.

Thyroid Nodules and Differentiated Thyroid Cancer, PTC patients are recommended for lateral lymph node dissection when there is clinical or radiographic evidence of lymph node metastasis (cN1b).⁷ The diagnosis of cN1b mainly relies on ultrasonography. However, studies have shown that the diagnostic sensitivity of colour Doppler ultrasound is only 66.38% for cervical lymph node metastasis.¹² Non-specific cervical lymph node lesions are usually found in ultrasound, which makes clearly distinguishing between PTC lymph node metastasis stages cN0 and cN1b difficult. In the treatment process of our hospital, central lymph node dissection is routinely performed, and prophylactic lateral cervical lymph node dissection is

TABLE 5 Details of skip lateral lymph node metastasis.

Case no.	Sex	Age	Tumour size (cm)	ETE	Multifocality	Location
1	Female	30	1.30	No	No	Upper
2	Female	56	0.80	Yes	No	Upper
3	Female	60	0.20	Yes	No	Middle
4	Female	19	2.20	Yes	No	Upper
5	Female	51	1.00	Yes	No	Upper
6	Female	57	0.80	Yes	Yes	/

Abbreviations: ETE, extrathyroidal extension.

usually not used as a standard treatment. Therefore, determining the indication of lateral cervical lymph node dissection is a problem that needs to be solved by clinicians.

The results of this study showed that in all patients with PTC who underwent initial surgery, the LLNM rate was 13.4%. The maximum diameter primary of the tumour > 2 cm, ETE and CLNM were independent risk factors for LLNM, which were significantly different from those of CLNM.¹³⁻¹⁸ The maximum diameter of primary tumours was not an independent risk factor for CLNM.¹⁵ The number of independent risk factors found in this study was smaller than that in the meta-analysis of other researchers.¹⁹⁻²¹ In the meta-analysis by So, Y. K et al.,¹⁹ CLNM, ETE, tumour size, multifocality, male sex, tumour location, and bilateral primary tumours were independent risk factors for LLNM.

Among the three independent risk factors in this study, the risk degree of ETE was the highest (OR = 5.202). According to the 8th edition of the American Joint Committee on Cancer (AJCC) guidelines, the importance of ETE is more prominent in the grouping of prognostic factors. As long as there is ETE of the primary tumour, the TNM grade is T3b, which is more dangerous than primary tumours >4 cm but limited in the thyroid capsule (T3a). In this study, the risk factor of ETE was also higher than the maximum diameter of the primary tumour (OR = 3.880), consistent with the 8th Edition AJCC guidelines. CLNM was also an independent risk factor for LLNM. In addition, as the CLNM number increases to greater than 5, the risk of LLNM increases, similar to the findings of Spinelli C.¹⁷ For PTC, primary tumour > 2 cm, ETE and CLNM are characteristics of greater aggressiveness. Consequently in future research, these related greater aggressiveness variables should be included when studying a new risk factor, such as genetic markers, thus perhaps these could be part of the decision to accompany the total thyroidectomy with a lymphadenectomy.

HT is a common autoimmune disease in thyroid dysfunction and often appears synchronously with PTC. The association between HT and PTC remains controversial.²²⁻²⁴ Some studies have also studied the relationship between HT and lymph node metastasis, in which a greater number of studies suggests that HT has little to do with lymph node metastasis.²⁵⁻²⁸ In our study, there was no significant correlation between HT and LLNM.

Among 209 patients with PTC, 6 patients had skip LLNM. In general, the lymph node metastasis of PTC presents a stepwise

spread pattern: first, it transfers to the central lymph node and subsequently to the lateral cervical compartment.²⁹ The condition of LLNM without CLNM is called skip LLNM. Skip LLNM is a non-negligible problem in the clinic. According to an analysis by other researchers,^{30,31} all primary lesions with skip LLNM were located in the upper thyroid gland, which was similar to the findings of our study.

However, there are some shortcomings in this study. For example, the metastases of lateral cervical lymph nodes are not recorded by anatomic lymph node compartment boundaries. The AJCC guidelines suggest that small lymph node metastasis has little effect on prognosis, but there is no data on the size of the metastatic lymph nodes in this retrospective study. Additionally, the specific location data of the primary tumours are not fully recorded. These are the issues that need to be addressed in clinical settings in the future.

In summary, the LLNM of PTC is associated with the diameter of the primary tumour > 2 cm, ETE and CLNM. According to this study, before or during the operation, if the following situations are encountered, we recommend lateral cervical lymph node dissection. First, preoperative cervical color Doppler ultrasound was highly suspected of LLNM, in addition, the tumour > 2 cm or ETE or CLNM was found during the operation. Second, the pathological results of the lateral cervical lymph node puncture were positive for metastasis. Third, preoperative cervical color Doppler ultrasound examination did not suspect LLNM. However, it was found that tumour > 2 cm, ETE and CLNM coexisted during the operation. If at least one of the above conditions is met, consider lateral cervical lymph node dissection.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Ethics approval for the study was given by ethics committee of Beijing Friendship Hospital, Capital Medical University.

CONSENT FOR PUBLICATION

We have received consents from individual patients who have participated in this study. The consent forms will be provided upon request.

COMPETING INTERESTS

The authors declare that they have no competing interests.

AUTHORS CONTRIBUTIONS

Qiang Liu, Liang-Fa Liu design and write the article. Ming-Hang Yu, Xue-Feng Huang data analysis. Qiang Liu, Wen-Ting Pang, Yan-Bo Dong, Zhen-Xiao Wang clinical data collection.

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Not applicable.

DATA AVAILABILITY STATEMENT

The datasets analysed during the current study are available in the Research Registration repository, <https://www.researchregistry.com>. Research registration number: Researchregistry5081.

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