

# Risk factors for lymph node metastasis of cN0 papillary thyroid carcinoma

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## Abstract

**Objective** To investigate the risk factors for cervical lymph node metastasis of clinically lymph node-negative (cN0) papillary thyroid carcinoma (PTC).

**Methods** Patients and Methods: The clinicopathologic data of patients with cN0 PTC who underwent at least one lobectomy plus central lymph node dissection at Xuzhou Central Hospital from January 2018 to December 2020 were retrospectively collected and the risk factors of lymph node metastasis analyzed. Univariate and multivariate analyses were performed to detect the risk factors for cervical lymph node metastasis.

**Results** A total of 312 patients with cN0 PTC were enrolled in this study. The postoperative pathology results showed that 134 patients (42.9%) had central lymph node metastasis, of whom 24 (17.9%) had lateral lymph node metastasis (LLNM). The univariate analysis results showed that male gender, age <45 years, tumor diameter ≥10 mm, bilateral cancer, capsule invasion, and multiple foci were associated with cervical lymph node metastasis of cN0 PTC ( $P < 0.05$ ). Further logistic regression analysis results showed that these factors, except age, were independent risk factors for cervical lymph node metastasis of cN0 PTC ( $P < 0.05$ ). The results also showed that the risk of LLNM increased with an increase in the number of positive central lymph nodes in patients with cN0 PTC ( $P < 0.05$ ).

**Conclusion** Cervical lymph node metastasis of cN0 PTC is related to many factors, and a high number of positive central lymph nodes indicates a high risk of LLNM. Patients with risk factors should undergo preventive central lymph node dissection at the first surgery, and in patients with a high number of positive central lymph nodes, lateral lymph node dissection should be discreetly performed.

**Key words:** papillary thyroid carcinoma; risk factor; complication

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Papillary thyroid carcinoma (PTC) is the most well-known type of thyroid cancer, accounting for over 80% of all thyroid carcinoma cases<sup>[1]</sup>. The prognosis of patients with PTC is favorable; their 10-year survival rate is over 95%<sup>[2]</sup>. Though PTC exhibits a favorable prognosis, relatively low malignancy, and positive response to surgery, central lymph node metastasis (CLNM) is very common in PTC; it has been observed in 20%–90% of patients<sup>[3–4]</sup>. CLNM not only increases the recurrence rate and reduces disease-free survival time but also elevates the rates of lateral lymph node metastasis (LLNM)<sup>[5]</sup>.

For the preoperative evaluation of patients suspected to have CLNM, central lymph node dissection (CLND) is strongly recommended in some guidelines. At present, contrast-enhanced computed tomography (CT) and neck ultrasound (US) are widely used for preoperative imaging to assess CLNM; unfortunately, the sensitivities of US

(23%–53.2%) and contrast-enhanced CT (41%–66.7%) are particularly not high enough for accurate evaluation<sup>[6, 7]</sup>. For patients with cN0 stage PTC, prophylactic cervical lymph node dissection (PCLND) is still controversial.

## Materials and methods

### Patients

A total of 312 patients at the Xuzhou Central Hospital from January 2018 to December 2020 were eligible for the study. All the patients had to meet the following criteria: (1) all suspected cases of PTC without evidence of CLNM following US or CT examination; (2) all patients with no history of neck radiation or previous neck surgery; (3) PTC should have been diagnosed by intraoperative frozen or postoperative pathological examination; (4) all patients at the least underwent unilateral thyroidectomy with

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CLND; 5) complete follow-up data.

### Treatment

For patients with PTC, CLND is routinely performed in our hospital. The ipsilateral lobe and isthmus were resected for unilateral primary lesions while total thyroidectomy was performed for multiple lesions and bilateral primary lesions. According to previous studies, the rate of LLNM was associated with an increase in CLNM and tumor size. In our research, LLNM occurs only if there is CLNM and tumor diameter  $\geq 10$  mm on intraoperative frozen pathology [8]. Central lymph nodes lie in the center of the neck; they include the prelaryngeal, pretracheal, and paratracheal lymph nodes. Cervical lymph nodes are divided into levels I, II, III, IV, V, and VI. After surgery, all patients with PTC received levothyroxine (L-T4) for thyroid-stimulating hormone (TSH) suppression. Some patients with advanced disease received iodine-131 treatment.

### Surgical complications

Total serum calcium and parathyroid hormone (PTH) levels were measured after surgery. The patients were considered to have permanent hypoparathyroidism when symptoms still existed or total serum calcium and PTH levels remained below the normal range for over half a year postoperatively. Direct fiber-optic laryngoscopy was performed to evaluate cord motility in all patients with PTC before and after surgery. The patients were considered to have permanent recurrent laryngeal nerve injury when the cord palsy remained unfixed for over half a year postoperatively.

### Statistical analysis

Univariate and multivariate analyses were performed to determine the significant clinical characteristics. Univariate analyses were performed using the chi-squared test. Variables with  $P < 0.05$  on univariate analysis were included for multivariate analysis. Multivariate analyses were performed using logistic regression analysis. The results were presented as odds ratios (OR) with 95% confidence intervals (CI) and  $P$  values. Differences associated with  $P < 0.05$  were considered statistically significant. Statistical analysis was performed using SPSS 13.0 software (SPSS Inc, Chicago, USA).

### Results

There were 312 patients enrolled in this study, including 217 females (69.6%) and 95 males (30.4%). Their median age at the time of PTC diagnosis was 46 years (ranged, 14–78 years). The tumor diameter ranged from 0.3–5.8 cm. A total of 139 patients had a tumor size  $\leq 10$  mm (44.6%), while 173 patients had a tumor size

$> 10$  mm (55.4%). There were 85 patients (27.2%) who exhibited multifocal disease and 227 (72.8%) had single lesions. There were 71 (22.8%) and 241 (77.2%) unilateral and bilateral tumors, respectively. Fifty-six patients had invasion of adjacent structures, such as the strap muscles, trachea, and recurrent laryngeal nerve. Thirty-eight patients had Hashimoto thyroiditis.

After the postoperative pathological examination, 134 (42.9%) patients were found to have CLNM, among whom 24 (17.9%) had LLNM. For 88 of the patients, the number of positive central lymph nodes was less than 3, and of these, only 11 had LLNM. For 46 of the patients, the number of positive central lymph nodes was greater than 3, and of these, 13 had LLNM. All patients with PTC underwent CLND. A total of 72 patients underwent both lobectomy and unilateral CLND. Total thyroidectomy combined with bilateral CLND was performed in 92 patients. Total thyroidectomy and unilateral CLND and LLND was performed in 87 patients. Total thyroidectomy combined with unilateral LLND and bilateral CLND was performed in 56 patients, and total thyroidectomy plus bilateral CLND and LLND was performed in 5 patients. The patients' surgery patterns are summarized in Table 1.

Univariate analysis revealed that male gender, age  $< 45$  years, tumor diameter  $\geq 10$  mm, bilateral cancer, capsule invasion, and multiple foci were associated with CLNM of cN0 PTC ( $P < 0.05$ ). Further logistic regression analysis results showed that these factors, except age, were independent risk factors for CLNM of cN0 PTC ( $P < 0.05$ ). While it was found that the risk of LLNM increased with an increasing number of positive central lymph nodes in patients with cN0 PTC ( $P < 0.05$ ) (Table 2 and 3), the  $\chi^2$  test revealed that CLNM was an important risk factor for LLNM ( $\chi^2 = 5.104$ ,  $P = 0.024$ ; Table 4).

Table 5 shows the postoperative complications. Fifty-six patients (17.95%) had transient hypoparathyroidism that resolved within 6 months and 9 (2.88%) had persistent hypoparathyroidism over 6 months. Ten patients had vocal cord palsy, which implied recurrent laryngeal nerve injury: 8 (2.56%) recovered within 1 to 6 months while the other 2 (0.64%) had persistent injury. One patient (0.32%) underwent reoperation because of postoperative bleeding. Four patients (1.28%) had chyle leakage, which was cured within 30 days. Complications such as, hematoma, wound infection, and tracheal leakage were observed in 12 patients.

**Table 1** Surgery pattern

Treatment	<i>n</i>
Lobectomy plus ipsilateral CLND	72
Total thyroidectomy plus bilateral CLND	92
Total thyroidectomy plus unilateral CLND and unilateral LLND	87
Total thyroidectomy plus bilateral CLND and unilateral LLND	56
Total thyroidectomy plus bilateral CLND and bilateral LLND	5

**Table 2** Univariate analysis of cervical lymph node metastasis in cN0 PTM patients

Variables	n	Cervical lymph node metastasis	$\chi^2$	P
Age (years)			4.1	0.043
≤ 45	131	65		
> 45	181	69		
Gender			9.191	0.002
Female	217	81		
Male	95	53		
Tumor diameter (cm)			8.539	0.003
≤1	139	47		
>1	173	87		
Bilateral neoplasms			9.852	0.002
No	241	92		
Yes	71	42		
Extrathyroid invasion			8.791	0.003
Yes	56	34		
No	256	100		
Multifocality			10.301	0.001
Yes	85	49		
No	227	85		
Thyroiditis			1.656	0.198
Yes	38	20		
No	274	114		

**Table 3** Multivariable analysis of cervical lymph node metastasis in cN0 PTM patients

Variables	standard error	Wald	95%CI	P
Age	0.249	1.946	0.434–1.151	0.163
Gender	0.271	6.870	0.288–0.836	0.009
Tumor diameter	0.255	11.304	1.431–3.895	0.001
Location	0.300	6.815	1.216–3.942	0.009
Multifocality	0.278	5.795	0.297–0.883	0.016
Extrathyroid invasion	0.322	7.349	0.223–0.785	0.007

**Table 4** Association between central lymph node metastasis and lateral lymph node metastasis

Central lymph node metastasis	n	Lateral lymph node metastasis		$\chi^2$	P
		Positive	Negative		
1–3	88	11	77	5.104	0.024
> 3	46	13	33		

**Table 5** The complications after operation

Complications	n	%
Transient hypoparathyroidism	56	17.95
Persistent hypoparathyroidism	9	2.88
Transient recurrent laryngeal nerve injury	8	2.56
Persistent recurrent laryngeal nerve injury	2	0.64
Chyle leakage	4	1.28
Bleeding	1	0.32
Others	12	3.85

## Discussion

Most patients with PTC have an excellent prognosis and a low mortality rate; however, PTC also shows a high potency to spread to cervical lymph nodes<sup>[9]</sup>. CLNM existed in 20%–90% of patients with PTC. The low sensitivities of CT and US lead to inaccurate preoperative assessment. Unidentified metastatic lymph nodes remain in the neck and become the main source of recurrence, making patients suffer from reoperation, recurrence, and disease-specific mortality. In our study, the CLNM occurrence rate was 42.9%, which is comparable to that in previous studies<sup>[10, 4]</sup>. We found male gender, tumor diameter ≥10 mm, bilateral cancer, capsule invasion, and multiple foci to be closely associated with the probability of CLNM, which is consistent with previous reports<sup>[11–13]</sup>. Currently, there are no new or more accurate indicators of CLNM.

Many studies have reported that age is a risk factor for CLNM. The cut-off age of 45 years is associated with a poor prognosis and increased recurrence, and it is widely used as a clinical marker for prognosis<sup>[14]</sup>. In multivariate analyses, we observed that age was not a significant risk factor for CLNM in patients with stage cN0 PTC. Some scholars have also observed a positive correlation between age younger than 45 years and a higher rate of CLNM, while others used 55 years as the cut-off age<sup>[15–16]</sup>.

There were 217 females (69.6%) and 95 males (30.4%) enrolled in this study. The central lymph nodes of 81 of the 217 female patients were positive while those of 53 of the 95 male patients were positive. The difference was statistically significant ( $P = 0.002$ ). Although the incidence of PTC was higher among women, the rates of CLNM were higher in men, who happened to be more prone to unhealthy lifestyles<sup>[17]</sup>.

As always, tumor size and capsule invasion are important factors in TNM staging and can, therefore be used to predict aggressiveness<sup>[18]</sup>. In our data, we found that tumor size >1 cm and capsule invasion exhibited a high association with the risk of CLNM in patients with cN0 PTC.

Multifocal PTC was always considered to involve intraglandular spread and be more aggressive than unifocal PTC. It was also reported that multiple tumors were associated with more aggressive clinicopathological features and a poor prognosis in patients with PTC<sup>[19]</sup>. Forty-nine of the 85 patients with multifocal disease had multifocal CLNM, while 85 of the 227 patients with single lesions had unifocal CLNM. The difference was statistically significant ( $P = 0.001$ ). We also observed that cN0 CLNM was associated with bilateral tumors. However, Sun *et al.*<sup>[20]</sup> reported that bilateral tumors were not a significant risk factor for CLNM in patients with cN0. Our data also showed that there was no correlation

between Hashimoto's thyroiditis and CLNM in patients with cNO.

There is still no uniform conclusion on CLND, and whether PCLND is needed remains controversial. The Japanese Association of Endocrine Surgeons (JAES) routinely recommends [21]. Performing PCLND provides the most real and adequate TNM staging, allows for speculation about the prognosis, and contributes to the decision whether to administer TSH suppressive therapy or radioactive iodine (RAI) therapy. It also decreases recurrence, increases disease-free survival, and reduces the thyroglobulin levels during postoperative follow-up. In addition, PCLND can help reduce the chances of reoperation and any other associated complications. Some scholars have suggested performing PCLND only in a selected group of patients with the recognized factors of higher locoregional recurrence [22]. The American Thyroid Association (ATA) guidelines suggest that PCLND should be routinely performed only in patients with advanced disease: stages T3 and T4 [23]. One reason why the ATA discourages PCLND is that CLNM seems to affect recurrence rather than disease-free survival and the other is that most thyroid surgeons in the United States are not considered to be competent enough in the procedure [24].

Some scholars insist that PCLND may increase the chances of complications and has no benefits of survival for patients with PTC. Kim SK *et al.* [25] suggested that PCLND may not be suggested in PTC due to the absence of increased survival time and clear evidence of complications. Nonetheless, reoperation due to recurrence in cervical lymph nodes is inevitably associated with postoperative complications, such as hypoparathyroidism and recurrent laryngeal nerve injury. Lymph node resection means wide dissection; it may result in temporary or permanent dysphonia in up to 1%–3% of cases [26]. In our study, there were 10 patients with vocal cord palsy, which implied recurrent laryngeal nerve injury: 8 (2.56%) recovered within 1 to 6 months while the other 2 (0.64%) had persistent damage. Clearance of all the fatty and lymphatic tissues around the parathyroid glands, which may be unintentional, could cause permanent or transient hypoparathyroidism in up to 2%–5% and 10%–50% of cases, respectively [27]. We reported that 56 patients (17.95%) had transient hypoparathyroidism and 9 (2.88%) had persistent hypoparathyroidism. Our results are consistent with the results from previous studies. It was reported in some previous papers that the incidence of chyle leakage ranges from 0.5%–8.3% [28], and in our study, 4 patients (1.28%) had chyle leakage and they were cured within a month. According to our study, routine PCLND did not increase the chances of complications, but it helped in avoiding the potential risk of a second operation and in defining a

more accurate stage.

We also found that there is a strong correlation between CLNM and LLNM. The incidence of LLNM increased with an increasing number of positive central lymph nodes. This can be explained by the dissemination of PTC. CLNM seldom occurs rapidly, and it tends to occur in a consecutive order from the central compartment to the lateral compartment lymph nodes. Chen *et al.* [16] reported in their study that 21 patients had skip metastasis, that is to say, there was LLNM with no CLNM. Hu *et al.* [29] reported that age >55 years, primary tumor located in the upper portion of the thyroid lobe, and unilaterality were associated with the risk of skip metastasis. The underlying mechanism of this form of metastasis is still unclear. In our study, there were 88 patients for whom the number of positive central lymph nodes was under 3, and of these, only 11 had LLNM. On the other hand, there were 46 patients for whom the number of positive central lymph nodes was greater than 3, and of these, 13 had LLNM. The difference was statistically significant ( $P = 0.024$ ).

## Conclusion

CLNM occurs frequently and it is not easy to detect preoperatively. Our results showed that there was an association between CLNM and male gender, tumor diameter  $\geq 10$  mm, bilateral cancer, capsule invasion, and presence of multiple foci. Patients whose number of positive central lymph nodes was greater than 3 were extremely prone to LLNM. The incidence of postoperative complications potentially caused by CLND was acceptable according to our study. Effectively assessing the risk factors for lymph node metastasis preoperatively is crucial for the development of individualized surgical plans. Routine PCLND does not increase the risk of postoperative complications and should be discreetly considered as a reasonable surgical treatment for patients with PTC.

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## Conflicts of interest

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## Author contributions

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## Data availability statement

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## Ethical approval

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