Original Article

Value of dissection of lymph nodes posterior to the right recurrent laryngeal nerve in patients with cN_0 papillary thyroid carcinoma

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Background: Tumor metastasis to lymph nodes posterior to the right recurrent laryngeal nerve (LN-prRLN) is a main cause of disease recurrence in patients with papillary thyroid carcinoma (PTC), which may increase the risk of recurrence and secondary surgery, and the disruption of normal anatomical relationships during secondary surgery increases the risk of laryngeal nerve injury and hypoparathyroidism. However, controversy remains as to whether the dissection of LN-prRLN is required in cN_0 PTC patients. The purpose of this study is to explore the factors associated with LN-prRLN metastasis in patients with cN_0 PTC and the need for LN-prRLN node dissection in patients with cN_0 PTC who undergo right central compartment dissection.

Methods: The clinical data of 290 patients with cN_0 PTC who received radical thyroid cancer surgery from December 2019 to March 2022 at our center were retrospectively analyzed. All the patients underwent thyroid lobectomy and right central lymph node dissection (CLND), along with other treatments. SPSS 26.0 statistical software was used for the analysis. The measurement data were compared using the rank-sum test, and the count data were compared using the chi-square test.

Results: LN-prRLN metastasis was detected in 65 (22.4%) of the 290 cN_0 PTC patients. The metastasis sites included level VIa (51.72%), the left central compartment (22.76%), and the prelaryngeal compartment (8.97%). The univariate analysis revealed that tumor multifocality, a tumor diameter >1 cm, capsular invasion, LN metastasis in the left central compartment, and level VIa positivity were influencing factors of LN-prRLN metastasis in PTC patients. The logistic regression analysis showed that a tumor diameter >1 cm (OR =2.897, 95% CI: 1.630–5.147, P<0.001), LN metastasis in the left central compartment (OR =3.724, 95% CI: 2.039–6.801, P<0.001), and level VIa (OR =3.405, 95% CI: 1.846–6.281, P<0.001) positivity were independent risk factors of LN-prRLN metastasis in PTC patients.

Conclusions: The high-risk factors of LN-prRLN metastasis in cN_0 PTC patients include a large tumor (a diameter >1 cm), lymph node metastasis in the left central compartment, and lymph node metastasis in level VIa. For patients with cN_0 PTC undergoing right CLND, with high-risk factors of LN-prRLN metastasis, LN-prRLN dissection is recommended.

Keywords: Papillary thyroid carcinoma (PTC); lymph nodes posterior to the right recurrent laryngeal nerve (LN-prRLN); central compartment lymph node dissection; risk factor

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Introduction

As one of the most common malignant tumors in head and neck surgery, papillary thyroid carcinoma (PTC) accounts for approximately 90% of all thyroid malignancies, and its incidence continues to rise globally (1). PTC has a good prognosis and progresses slowly, with a 10-year survival rate of over 90% (2). However, cervical lymph node (LN) metastasis can occur in the early stage of PTC, among which the central compartment (level VI) is the 1st echelon of nodal metastases, with a metastasis rate of 20–80%, which was related to the recurrence and survival of patients with PTC (3). Surgery is the mainstay of treatment for PTC patients, for which cervical lymph node dissection (CLND) is a key technique. For patients with definite central LN metastasis before surgery, the role of central compartment dissection (CCD) has been well established. However, controversy remains as to whether CCD is feasible for cN_0 PTC patients.

The guidelines on the diagnosis and treatment for persistent/recurrent and metastatic differentiated thyroid cancer of the Chinese Society of Clinical Oncology (CSCO) recommend ipsilateral CCD for cN_0 PTC if the technical conditions allow. Conversely, the guidelines of the American Thyroid Association state that prophylactic CLND in cN_0 PTC cannot improve long-term survival and may even increase the incidence of complications (4). However, those who are of the view that CCD can lower the local recurrence rate and reduce re-resection, advocate for the radical treatment of PTC (5).

Postoperative pathology can significantly improve the accuracy of tumor, node, metastasis (TNM) staging, which in turn enables the development of individualized treatment regimens (6). With the recurrent laryngeal nerve (RLN) as a boundary, the right central compartment can be divided into the right RLN superficial LNs (level VIa) and the LNs posterior to the right recurrent laryngeal nerve (LN-prRLN) (7).

LN-prRLNs are deeply located and have an anatomically narrow space, which makes the preoperative prediction of LN metastasis much more difficult. During CCD, most surgeons do not perform LN-prRLN dissection, both because it is neglected without sufficient attention and because performing LN-prRLN exploration may increase the risk of recurrent laryngeal nerve injury. Surgeons should integrate preoperative and intraoperative risk factors for LN-prRLN metastasis, balance the benefits and risks of surgery when making surgical decisions, and minimize the occurrence of surgical complications. LN-prRLN metastasis is not uncommon in PTC patients, with a reported metastasis rate of up to 26.6% (8), and it is also the main cause of PTC recurrence. In addition, in the recurrence patients, re-surgical dissection of the metastatic LN-prRLN is more difficult due to disruption of normal anatomy and may increase the risk of complications such as temporary vocal cord paralysis, hypoparathyroidism, and permanent hypoparathyroidism. Therefore, for patients with cN_0 PTC, the initial LN-prRLN dissection has a certain value in reducing local recurrence and the risk of reoperation, and improving prognosis. In this study, we retrospectively explored the risk factors affecting LN-prRLN metastasis in 290 cN_0 PTC patients to provide reference for surgical dicisions in patients with cN_0 PTC and to help surgeons assess the necessity of LN-prRLN dissection in patients with cN_0 PTC who require right CCD. We present the following article in accordance with the STARD reporting checklist (available at https://gs.amegroups.com/article/view/10.21037/gs-22-337/rc).

Methods

General data

The clinicopathological data of 551 PTC patients who received radical thyroid cancer surgery at the Department of Breast and Thyroid Surgery of our center from December 2019 to March 2022 were retrospectively reviewed. The preoperative evaluation included ultrasonography (US) of the thyroid and cervical lymph nodes, computed tomography (CT) of the neck, serum electrolytes, thyroid function test, a test for thyroid-related antibodies, thyroglobulin (TG), thyroid stimulating hormone (TSH), parathyroid hormone (PTH), and video laryngoscopy. All patients underwent US and CT examinations to assess lymph node metastasis, and the examination results were clear in 513 patients without preoperative lymph node involvement. The electronic laryngoscopy was used to assess patients for vocal cord paralysis before surgery. Among them, 290 patients had cN_0 disease and had undergone LN-prRLN dissection. All the operations were completed by the same surgical team.

The pathological examination of surgical specimens included intraoperative frozen sections and postoperative paraffin-embedded sections. The pathological diagnosis was completed by pathologists with qualifications of associate chief physician or above, and pathology reports were issued.

The pathological findings of all patients were confirmed as PTC by intraoperative frozen sections and postoperative paraffin sections. The tumors were considered to be multifocal if ≥2 lesions were found in the glandular lobes. The largest diameter was taken as the tumor diameter in PTC. The patients were divided into the following 2 groups based on whether the LN-prRLN had metastasized: (I) the nodal metastasis group; and (II) the non-nodal metastasis group. According to the criteria of the World Health Organization (WHO), papillary thyroid microcarcinoma was defined as thyroid cancer measuring ≤1.0 cm in its greatest dimension; thus, 161 patients were divided into the ≤1 cm group and the >1 cm group. Based on the American Joint Committee on Cancer Staging guidelines, the patients were divided into the following 2 age groups: <55 years and ≥55 years (9). The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013) and was approved by the Ethics Committee of the Hunan Provincial People's Hospital (approval No. 2021-140). Individual consent for this retrospective analysis was waived.

Surgical treatment

All the patients underwent routine preoperative examinations to rule out surgical contraindications and to check for hoarseness and vocal cord paralysis. The patients were asked to lie in the prone position with their neck elevated and extended. The endotracheal intubation was performed under general anesthesia. An arc-shaped incision was created 2 fingers above the sternal notch, through which the skin, soft tissue, and platysma were incised to mobilize the skin flap and expose the thyroid glands. The resection of the primary lesions (i.e., the resection of the affected gland lobe plus an isthmus or bilateral thyroid lobectomy) was performed concurrently with the CCD. More specifically, a total thyroidectomy plus bilateral CLND was performed in 138 cases, a total thyroidectomy plus right CLND was performed in 80 cases, and a resection of right gland lobe and isthmus plus right CLND was performed in 72 cases. Thus, 152 patients did not receive left CLND. A total of 17 patients had left PTC accompanied by right thyroid nodules.

If the rapid intraoperative pathological examination results showed PTC at the right lobe, and the nanocarbon staining showed suspicious metastasis at the right central LNs, right CLND was performed. The LNs in level VIa (i.e., all the central lymphatic and fatty tissues in the superficial layer of the right RLN, including the perithyroid LNs, pretracheal LNs, and Delphian LNs) were first dissected with the upper border at the level of the hyoid bone, the lower border at the superior edge of the innominate artery, the inner border at the inner side of the left inferior thyroid vein, and the outer border at the inner edge of the common carotid artery. The LN-prRLN (level VIb) was dissected with the upper border at the location at which the right RLN enters the larynx, the lower border at the junction between the innominate artery and tracheoesophageal groove (the deep layer is the cupula pleuralis), the medial boundary at the right edge of the tracheoesophagus, the lateral border at the medial edge of the common carotid artery, and the deep surface reaching the deep layer of the deep cervical fascia (prevertebral fascia) (10).

Statistical analysis

The data were analyzed using SPSS 26.0 statistical software package. Age and tumor diameter were continuous variables with skewed distributions; thus, these variables are presented as the mean ± standard deviation and were compared using a rank-sum test. The number of LNs dissected showed a skewed distribution, and this variable is presented as the median. The count data (i.e., gender, capsular invasion, and tumor multifocality) were compared using the chi-square test.

First, the correlations between the clinicopathological parameters and LN-prRLN metastasis were evaluated by a univariate analysis. The statistically significant factors were then included in the logistic regression analysis. Second, the logistic regression model was used to fit the covariates to generate a new predictor covariate. The receiver operating characteristic (ROC) curves were used to evaluate the predictive values, optimal cut-off values, sensitivities, and specificities of potential high-risk clinical factors and predictor covariates. A P value of <0.05 was considered statistically significant.

Results

Clinical data of 290 patients with cN_0 PTC

Of the 290 patients, 218 (75.2%) were female and 72 (24.8%) were male. The patients were aged 19–68 years (42.2±10.67 years). The tumors ranged in size from 0.8–50 mm (11.62±7.75 mm). The tumors were on the right side in 165 cases, the left side in 17 cases, and bilateral

Table 1 LN metastasis in different regions of PTC patients

Tumor location	Left central compartment, n (%)	Prelaryngeal compartment, n (%)	Level VIa, n (%)	LN-prRLN, n (%)
Right-sided PTC [165]	11 (6.67)	10 (6.06)	81 (49.09)	34 (20.61)
Left-sided PTC [17]	8 (47.06)	3 (17.65)	7 (41.18)	3 (17.65)
Bilateral PTC [108]	47 (43.52)	13 (12.04)	62 (57.41)	28 (25.93)

PTC, papillary thyroid carcinoma; LN-prRLN, lymph node posterior to the right recurrent laryngeal nerve; level VIa, the right recurrent laryngeal nerve superficial lymph node; LN, lymph node.

in 108 cases. The lesions were multiple in 133 cases and solitary in 157 cases. The lesions were accompanied by a nodular goiter in 27 cases and Hashimoto's thyroiditis in 43 cases. LN-prRLN metastasis occurred in 65 cases.

Regional LN dissection and metastasis

Among the 290 PTC patients, the median number of LNs dissected in level VIa, LN-prRLN, and the right central compartment were 7, 10, and 17, respectively. The rate of LN metastasis was 51.72% (150/290) in level VIa and 22.41% (65/290) in LN-prRLN. The rate of LN metastasis in LN-prRLN was higher in patients with right or bilateral PTC than in patients with left PTC. The metastasis rate was 22.76% (66/290) in the left central compartment and 8.97% (26/290) in the prelaryngeal compartment (see *Table 1*).

Correlation between LN-prRLN metastasis and the clinicopathological features of PTC

Univariate analysis of LN-prRLN metastasis and the clinicopathological features of PTC

In the 290 PTC patients, LN-prRLN metastasis was found to be statistically correlated with tumor multifocality, a tumor diameter >1 cm, capsular invasion, and LN metastasis in the left central compartment and level VIa (all $P<0.05$). However, no significant correlations were found between LN-prRLN metastasis and gender, age, nodular goiter, Hashimoto's thyroiditis, and LN metastasis in the prelaryngeal compartment (all $P>0.05$). Thus, tumor multifocality, a tumor diameter >1 cm, capsular invasion, and LN metastasis in the left central compartment and level VIa were the influencing factors of LN-prRLN metastasis in PTC patients (see *Table 2*).

Multivariate analysis of LN-prRLN metastasis and the clinicopathological features of PTC

The logistic regression analysis of the above influencing factors (including tumor multifocality, a tumor diameter >1 cm, capsular invasion, LN metastasis in the left central compartment, and level VIa) indicated that LN-prRLN metastasis was closely related to a tumor diameter >1 cm (OR =2.897, 95% CI: 1.630–5.147, $P<0.001$) and LN metastasis in the left central compartment (OR =3.724, 95% CI: 2.039–6.801, $P<0.001$) and level VIa (OR =3.405, 95% CI: 1.846–6.281, $P<0.001$). However, no significant correlations were found between LN-prRLN metastasis and the multifocality of tumor and capsular invasion (all $P>0.05$). Thus, a tumor diameter >1 cm and LN metastasis in the left central compartment and level VIa were the independent risk factors of LN-prRLN metastasis in PTC patients (see *Table 3*).

Discussion

PTC has a good prognosis; however, some early stage PTC may metastasize to the cervical LNs and other distant areas. The most common site for nodal metastasis from PTC is the central compartment. The central compartment LNs are located around the trachea, and their superficial surface is covered by the thyroid. Due to their hidden locations and the effect of gas inside the trachea, abnormally enlarged LNs in the central compartment are often difficult to detect, even by preoperative ultrasound. In most patients, LN metastasis is often difficult to determine in the preoperative physical examination and imaging examinations (11). Thus, LNs in this area have become a common recurrence and a site of metastasis. It has been reported that the LN metastasis rate in the central compartment is 20–80% (12). Similarly, in the current study, the LN metastasis rate in the right central compartment was 54.14% (3).

Notably, the left and right central compartments are anatomically different, and the right and left RLNs have different routes to the larynx. The left RLN lies on the esophagus and ascends; thus, the LNs in the left central compartment are located in the superficial layer of the left

Table 2 Univariate analysis of LN-prRLN metastasis and the clinicopathological features of PTC

Variables	LN-prRLN		Metastasis rate (%)	χ^2	P value
	Metastasis	Non-metastasis			
Gender					
Male	16	56	22.22	0.002	0.964
Female	49	169	22.48		
Age (years)					
Mean ± SD	40.53±10.59	42.84±10.54			0.149
≥55	7	31	18.42	0.401	0.527
<55	58	194	23.02		
Tumor multifocality					
Multiple	38	95	28.57	5.356	0.021
Solitary	27	130	17.20		
Tumor diameters (cm)					
Mean ± SD	1.44±0.89	1.08±0.71			0.000
>1	42	87	32.56	13.750	0.000
≤1	23	138	14.29		
Capsular invasion					
Yes	37	93	28.46	4.956	0.026
No	28	132	17.50		
LNs in level VIa					
Metastasis	48	102	32.00	16.419	0.000
Non-metastasis	17	123	12.14		
LNs in prelaryngeal compartment					
Metastasis	7	19	26.92	0.334	0.563
Non-metastasis	58	206	21.97		
LNs in the left central compartment					
Metastasis	28	38	42.42	19.675	0.000
Non-metastasis	37	187	16.52		
Accompanied by a nodular goiter					
Yes	6	21	22.22	0.001	0.980
No	59	204	22.43		
Accompanied by Hashimoto's thyroiditis					
Yes	6	37	13.95	2.078	0.149
No	59	188	23.89		

PTC, papillary thyroid carcinoma; LN-prRLN, lymph node posterior to the right recurrent laryngeal nerve; LN, lymph node; level VIa, the right recurrent laryngeal nerve superficial lymph node; SD, standard deviation.

Table 3 Logistic regression analysis of the risk factors of LN-prRLN metastasis in PTC patients

Risk factor	β	SE	Wals	P	OR (95% CI)
Tumor multifocality	0.213	0.326	0.425	>0.05	1.237 (0.653, 2.345)
Capsular invasion	0.060	0.328	0.033	>0.05	1.061 (0.559, 2.017)
Tumor diameter	1.064	0.293	13.148	<0.001	2.897 (1.630, 5.147)
LN metastasis in the left central compartment	1.315	0.307	18.312	<0.001	3.724 (2.039, 6.801)
LN metastasis in level VIa	1.225	0.312	15.382	<0.001	3.405 (1.846, 6.281)

PTC, papillary thyroid carcinoma; LN-prRLN, lymph node posterior to the right recurrent laryngeal nerve; LN, lymph node; level VIa, the right recurrent laryngeal nerve superficial lymph node; OR, odds ratio; CI, confidence interval.

RLN. The space between the right RLN and the esophagus is filled with adipose and lymphoid tissues, and LNs in the right central compartment are divided into superficial and deep layers with the RLN as the boundary (13). During LN dissection, the LN-prRLN is often neglected due to its deep anatomical location, extensive and abundant blood supply (which covers up the LNs), and the operator's fear of injuring the RLN and/or unawareness of its importance. The insufficient dissection of LNs in the right central compartment results in residual LN metastasis, and the incomplete dissection of metastatic LNs is an important cause of recurrence (14,15). A 2nd operation may be required, during which the normal anatomical structures may be damaged, which increases the risks of RLN injury and hypoparathyroidism (16,17).

In the current study, we retrospectively analyzed the clinical data of 290 patients with cN_0 PTC. All the patients underwent thyroid surgery and CLND. We attempted to summarize the metastasis rate and characteristics of the LNs in the different cervical compartments and explore the influencing factors and risk factors of LN-prRLN metastasis. We also analyzed the value of LN-prRLN dissection in patients requiring CLND and sought to identify the populations that might benefit from this procedure.

The rate of lymph node metastasis was 54.14% in the right central compartment, 51.72% (150/290) in level VIa, and 22.41% (65/290) in the LN-prRLN in the cases included in this study. A univariate analysis was performed to determine the influencing factors of LN-prRLN metastasis. Additionally, a multivariate logistic regression analysis was performed to eliminate the confounding factors and identify the independent risk factors of LN-prRLN metastasis. Notably, only 17 (5.86%) of the 290 patients had LN-prRLN positivity (without level VIa positivity), which is known as skip metastasis (18), and requires special attention. Thus, for cN_0 PTC patients requiring central compartment dissection, the removal of the superficial LNs along the right RLN is not enough, and LN-prRLN dissection should be considered. The guidelines of the American Thyroid Association specifically state that the right CCD should include lymph nodes in the adipose tissue behind the RLN (4). Lee *et al.* noted that thyroid tumors in the right lobe were significantly associated with lymph node metastasis in the LN-prRLN (19). In this study, the rate of LN-prRLN metastasis was higher on the right (20.61%) than on the left (17.65%), so tumors on the right was more likely to metastasize to the LN-prRLN than the left. Notably, among the three patients with left PTC who developed LN-prRLN metastasis in this study, one patient had only cancer in left lobe, and Zhang *et al.* also reported that two cases with only lesion in left lobe were diagnosed with LN-prRLN metastasis, suggesting that we still need to pay attention to LN-prRLN metastasis in patients with PTC (13).

Thus, tumor multifocality, a tumor diameter >1 cm, capsular invasion, LN metastasis in the left central compartment and level VIa were the influencing factors of LN-prRLN metastasis in PTC patients. Among these, a tumor diameter >1 cm and LN metastasis in the left central compartment and level VIa were the independent risk factors of LN-prRLN metastasis in PTC patients. In this study, univariate analysis showed that tumor multifocality and capsular invasion were correlated with LN-prRLN metastasis, whereas multivariate analysis showed no significant correlation, which may be due to the small number of cases or the presence of other confounding factors.

Larger tumors may be more aggressive, and tumor size and local invasion are related to tumor (T) stage and thus to LN metastasis (20). Tumor diameter is considered an independent risk factor of LN-prRLN metastasis in

PTC (all P<0.05). According to WHO's criteria, papillary thyroid microcarcinoma in our current study was defined as PTC with the largest dimension of ≤1.0 cm. The rates of LN-prRLN were 32.56% and 14.29% in the >1 cm group and ≤1 cm group, respectively (P<0.05), which suggests that a larger tumor size is associated with a higher LN-prRLN metastasis rate. Both the univariate and multivariate analyses showed that the largest diameter of PTC was closely related to LN metastasis and local tumor invasion. LN-prRLN dissection is recommended for patients with >1 cm of cN_0 PTC.

We also found that the LN metastasis rates were 51.72% (150/290) in level VIa and 22.41% (65/290) in LN-prRLN. The probability of LN-prRLN metastasis in PTC patients with LN metastasis in level VIa was 32.00% (48/150), while the probability of LN-prRLN metastasis in PTC patients without LN metastasis in level VIa was only 12.14% (17/140) (P<0.05). A further analysis showed that the number of positive LNs in level VIa was positively correlated with the rate of LN-prRLN metastasis. Therefore, determining the status of lymph nodes in level VIa is beneficial for surgeons to clarify whether to perform LN-prRLN dissection (21), and LN-prRLN dissection is necessary for PTC patients with LN metastasis in level VIa. Left central LN metastasis is a high-risk factor for LN-prRLN metastasis. LN-prRLN metastasis was detected in 28 (42.42%) of the 66 PTC patients with left central LN metastasis, but in only 37 (16.52%) of the 224 PTC patients without left central LN metastasis (P<0.05). Therefore, LN metastasis in the left central compartment is a high-risk factor for LN-prRLN metastasis, and LN-prRLN dissection is necessary for patients with LN metastasis in the left central compartment. In this study, there were 290 patients without vocal cord paralysis or permanent hypoparathyroidism, including 61 patients (21.03%) with temporary hypoparathyroidism and 17 patients (5.86%) with reduced serum calcium levels. The intraoperative use of nano-carbon can avoid missing suspicious lymph nodes at hidden sites, and can effectively identify the parathyroid glands, increase the protection of the parathyroid glands and the safety of surgery, and reduce the occurrence of postoperative complications.

In conclusion, LN-prRLN metastasis is not uncommon in PTC patients. In patients with cN_0 PTC requiring CLND, it is necessary to perform LN-prRLN dissection when the patient has high-risk factors affecting LN-prRLN metastasis (tumor diameter >1 cm and LN metastasis in level VIa and left central compartment), LN-prRLN dissection is recommended after proper measures have been taken to protect the RLN from being injured during the operation. Notably, due to its single-center retrospective design, the current study was limited by the short analysis period, small sample size, and the lack of survival outcomes. Thus, the question of whether LN-prRLN dissection improves the long-term survival of patients requires long-term follow-up research.

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Footnote

Reporting Checklist: The authors have completed the STARD reporting checklist. Available at https://gs.amegroups.com/article/view/10.21037/gs-22-337/rc

Data Sharing Statement: Available at https://gs.amegroups.com/article/view/10.21037/gs-22-337/dss

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://gs.amegroups.com/article/view/10.21037/gs-22-337/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 conducted in accordance with the Declaration of Helsinki (as revised in 2013) and was approved by the Ethics Committee of the Hunan Provincial People's Hospital (approval No. 2021-140). Individual consent for this retrospective analysis was waived.

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