Cancer Control
Volume 30: 1–7

DOI: 10.1177/10732748221149819
journals.sagepub.com/home/ccx
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Lymph Node Posterior to the Right Recurrent Laryngeal Nerve Metastasis in Right Lobe T1a Papillary Thyroid Carcinoma: A Retrospective Cohort Study

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Abstract

Introduction and Objectives: This study analyzed the incidence and predictors of lymph node posterior to the right recurrent laryngeal nerve metastasis in T1a papillary thyroid carcinoma of the right lobe.

Methods: This was a retrospective cohort study. Patients were selected from those who had received surgical treatment for primary papillary thyroid carcinoma between January 2019 and December 2020. The association between clinicopathologic variables and lymph node posterior to the right recurrent laryngeal nerve metastasis was assessed using univariate and multivariate analyses. Postoperative complications were also described.

Results: Lymph node posterior to the right recurrent laryngeal nerve metastasis was present in 6.0% of the 402 study patients. It was the most likely to occur when there were other lymph node metastases, particularly in the lymph node anterior to the recurrent laryngeal nerve. Independent predictors for lymph node posterior to the right recurrent laryngeal nerve metastasis were a tumor size of ≥5.0 mm, a lower pole location, and lymph node anterior to the right recurrent laryngeal nerve metastasis. The rate of persistent vocal cord paralysis was .5%, and no patient developed permanent hypoparathyroidism.

Conclusions: Although lymph node posterior to the right recurrent laryngeal nerve metastases of the right lobe T1a papillary thyroid carcinoma is uncommon, the possibility of metastasis should be investigated when there is a positive lymph node anterior to the right recurrent laryngeal nerve in a tumor >5.0 mm in size located in the lower pole. Lymph node posterior to the right recurrent laryngeal nerve dissection is recommended for such tumors.

Keywords

lymph nodes, metastasis, thyroid papillary carcinoma, surgical dissection, tumor location

Introduction

Papillary thyroid carcinoma (PTC), the most common malignant tumor in the endocrine system, has a high detection rate, most likely due to improved diagnosis using high-resolution ultrasonography.[1] PTC is characterized by lymph node (LN) metastasis, and positive central LNs have been observed in >50% of patients with clinically negative central LN (cN0) PTC.[2] Guidelines by the American Thyroid Association (ATA) and Chinese Thyroid Association (CTA) have highlighted the significance of dissecting level VI in PTCs.[3,4] However, neither set of guidelines clarify the extent of dissection needed for the LN posterior to the right recurrent laryngeal nerve (LN-prRLN). The LN-prRLN is an important part of the central LNs, and several studies have identified the

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risk factors for LN-prRLN metastasis, including a tumor size >1 cm, multifocality, capsular invasion, extrathyroidal invasion, lateral neck LN metastasis, and LN anterior to the right recurrent laryngeal nerve (LN-arRLN) metastasis.[5,6] However, for T1a PTC cases, which represent >60% of newly diagnosed PTCs,[7] the efficacy of LN-prRLN dissection remains unknown.

Therefore, this study aimed to analyze the incidence of LN-prRLN metastasis, and the specific goal was to determine the predictors of LN-prRLN metastasis in right lobe T1a PTC cases. We hypothesized that tumor size and tumor location might be associated with the presence of positive LN-prRLN.

Materials and Methods

This study was approved by our Institutional Research Committee (LC20210533, May 5, 2021), and all participants signed a written informed consent before enrollment in the study. All procedures involving human participants were conducted in accordance with the 1964 Helsinki Declaration.

This was a retrospective cohort study, the reporting of this study conforms to STROBE guidelines,[8] and all patients details were de-identified. The medical records of consecutive patients (aged >18 years) who underwent surgical treatment for primary PTC were reviewed retrospectively between January 2019 and December 2020. Inclusion criteria comprised the following: (i) a PTC diagnosis staged as T1a, according to the American Joint Committee on Cancer (AJCC) 8th Classification, and confirmed by postoperative pathology; (ii) the neck was staged as cN0; (iii) according to preoperative ultrasound, there was only one malignant nodule (TI-RADS ≥4) on the right lobe and no suspicious malignant nodules (TI-RADS ≤3) were present in the left lobe or the isthmus. Exclusion criteria comprised a history of neck radiotherapy and neck surgery. Clinical data, including patient demographics, pathological findings (including lymphovascular invasion [LVI]), BRAF 600E mutation, and postoperative complications, were extracted and analyzed.

A right lobe PTC was defined as a tumor having a medial boundary, without involvement of the lateral tracheal border. Tumor locations were divided into the upper pole (ie, the upper part of the high plane of the isthmus), the middle third (ie, parallel to the isthmus), and the lower pole (ie, the lower part of the low plane of the isthmus).[9] A cN0 neck was defined as a neck without the following ultrasound features: a round shape, an echogenic hilum, microcalcification, peripheral blood flow on color Doppler images, and cystic changes,[6,10] and without the following computerized tomography features: a ratio of the longest to the shortest diameter of ≤2; an area with clear evidence of non-fat, low-density, or liquid components; and the largest diameter being >15 mm at level II and >10 mm at the other levels.[11] The tumor size was determined in relation to the longest tumor diameter. Transient hypoparathyroidism was defined as hypoparathyroidism occurring for <6 months after surgery, whereas permanent hypoparathyroidism was that which continued for >6 months postoperatively.[12]

All patients underwent preoperative neck ultrasound and computed tomography examinations. Intraoperative nerve monitoring was not routinely performed. According to the CTA guidelines, the extent of resection should be minimized to include the right lobe and the right central LNs.[4] The scope of LN-prRLN dissection was bounded by the RLN superficially, by the suprasternal fossa inferiorly, by the hyoid bone superiorly, and by the prevertebral fascia posteriorly. Surgical specimens of the central LNs were divided into four groups: LN-arRLN, LN-prRLN, prelaryngeal LN, and pretracheal LN. These specimens were sent for pathological examination individually.

The continuous variable was presented as mean ± standard deviation, and the categorical variable was presented as frequency. The primary outcome variable was LN-prRLN metastasis, the potential predictive variables included age (<55 vs ≥55 years), sex, tumor size (0-5.0 mm vs 5.0-10.0 mm), coexistent Hashimoto's thyroiditis, tumor location, number of malignant foci (1 vs 2), capsular invasion, and LVI. A chi-square test (univariate analysis) was used to evaluate the association between potential predictive variables and LN-prRLN metastasis. Significant factors in the univariate analysis were then analyzed using multivariate analysis (logistic regression analysis) to identify independent predictors. All statistical analyses were performed using SPSS version 20.0 software, and statistical significance was set at a P-value of <.05.

Results

Baseline Data

Of the 402 patients included in this study, the mean age was 48 ± 15 years, 311 (77.4%) were female, and 91 (22.6%) were male. Comorbid Hashimoto's thyroiditis developed in 163 patients (40.5%). There were 117 (29.1%) patients with tumors in the upper pole, 122 (30.4%) with tumors in the middle third, and 163 (40.5%) with tumors in the lower pole. The mean tumor size was 5.5 ± 1.8 mm. Postoperative pathological findings indicated that 51 (12.7%) patients had two malignant nodules, and there were no patients with three or more foci. Capsular invasion was present in 64 (15.9%) patients. LVI developed in 24 (6.0%) patients, and 282 (70.1%) patients had a BRAF 600E mutation. Total, sub-total, and unilateral thyroidectomies were performed for 27 (6.7%), 38 (9.5%), and 337 (83.8%) patients, respectively. All patients underwent a prophylactic right central neck dissection.

Central LN Metastasis

Central neck LN metastasis occurred in 94 (23.3%) patients, and the mean number of positive LNs was 1.5 (range, 1-6).

The most common metastatic pattern was isolated metastasis in the LN-arRLN, followed by simultaneous metastasis in the LN-arRLN and LN-prRLN. The least common metastatic pattern was simultaneous metastasis in the pretracheal LN, prelaryngeal LN, LN-arRLN, and LN-prRLN. There was no skip metastasis of isolated LN-prRLN metastasis (Table 1).

Association Between LN-prRLN Metastasis and Clinicopathologic Variables

LN-prRLN metastasis occurred in 24 (6.0%) patients. The LN-prRLN metastasis rate was 28.2% in patients with positive LN-arRLN, it was significantly higher than that in patients with negative LN-arRLN ($P < .001$). Of the 91 male patients, 13 (14.3%) had LN-prRLN metastasis, which was significantly higher than that observed in the female patients (3.5%; $P < .001$). Compared to patients with tumors <5.0 mm in size, those with tumors >5.0 mm had a LN-prRLN metastasis rate of 9.0%, and this difference was statistically significant ($P = .006$). In patients with tumors in the lower pole, the LN-prRLN metastasis rate was 11.0%, which was significantly higher than that in patients with tumors in the upper pole and the middle third ($P = .002$). No significant associations were noted between LN-prRLN metastasis and other clinicopathologic variables (Table 2; all $P > .05$). Upon further multivariate analysis, tumor size ($P < .001$, odds ratio [OR]: 2.794, 95% confidence interval [CI]: 1.265-6.558), tumor location ($P < .001$, OR: 2.007, 95%CI: 1.166-8.264), and LN-arRLN metastasis ($P < .001$, OR: 4.386, 95%CI: 1.932-10.556) were identified as the independent risk factors for LN-prRLN metastasis (Table 3).

Complications

Transient hypoparathyroidism was noted in 10 (2.5%) patients, all of whom underwent a total thyroidectomy; no patient developed permanent hypoparathyroidism. Voice change occurred in five (1.2%) patients immediately after the surgery; among them, two patients had persistent voice change with vocal cord paralysis, which was confirmed by laryngoscopy at the 14-, and 17-month postoperative follow-up. In the remaining three patients, the voice and normal vocal cord activity were regained within 6 months postoperatively. No patient developed chyle leakage; however, hematomas and wound infections developed in seven (1.7%) and 11 (2.7%) patients, respectively.

Discussion

A notable finding in this study was that LN-prRLN metastasis was not common in patients with right lobe T1a PTC, and that it only occurred in 6.0% of patients, and usually developed after LN-arRLN metastasis. The presence of a tumor ≥5.0 mm located in the lower pole was the apparent cause of LN-prRLN metastasis, and LN-prRLN dissection was found to be a relatively safe procedure in these patients.

Grodski et al.[13] first suggested that resection of the LN-prRLN should be included in routine central neck dissection. They also noted an increased risk of recurrent laryngeal nerve injury because the nerve was traced and elevated. Several studies have investigated the safety of LN-prRLN dissection and the incidence rate of and risk factors for LN-prRLN metastasis. Lee et al.[14] enrolled 123 patients with PTC, of whom 11.4% had LN-prRLN metastasis. They reported that a right lobe tumor, a tumor ≥10.0 mm in size, a lateral neck LN metastasis, and more positive central LNs were significantly associated with LN-prRLN metastasis. In a prospective study of 145 patients with differentiated thyroid carcinoma, Liu et al.[15] reported an 11.0% rate of LN-prRLN metastasis. The risk of positive LN-prRLN was higher when tumors showed multiplicity characteristics, when tumors were ≥10.0 mm in size, and when both LN-arRLN and right lateral LN metastasis were present. Neither of the previous studies undertook a multivariate analysis, and Liu's study included patients with follicular thyroid carcinoma, which typically has an extremely low LN metastatic tendency.

In a large-scale study by Luo et al.[16] involving 595 patients with PTC, 17.1% of the patients had LN-prRLN metastasis. The independent predictors for LN-prRLN metastasis included young age, large tumor size, capsular invasion, and right lateral LN metastasis. Pinyi et al.[17] undertook a study of 405 patients with PTC; they reported an LN-prRLN metastasis rate of 26.7%. Multivariate analyses identified a tumor size of ≥10.0 mm, multifocality, LN-arRLN metastasis, lateral neck LN metastasis, and extrathyroidal extension as significant factors for LN-prRLN metastasis. Similar findings have also been reported by Li et al.[18] and Chang et al.[19] The results of all

Table 1. Lymph Node (LN) Metastasis Pattern in the 94 Patients With Positive Central Lymph Nodes.

Metastatic sites	Number (%)
LN-arRLN[a]	50 (53.2%)
LN-arRLN + LN-prRLN[b]	21 (22.3%)
Prelaryngeal LN + LN-arRLN	11 (11.7%)
Pretracheal LN	9 (9.6%)
Pretracheal LN + Prelaryngeal LN + LN-arRLN + LN-prRLN	3 (3.2%)

[a]LN-arRLN: lymph node anterior to the right recurrent laryngeal nerve.
[b]LN-prRLN: lymph node posterior to the right recurrent laryngeal nerve.

Table 2. Univariate Analysis of the Predictors of Lymph Node Posterior to the Right Recurrent Laryngeal Nerve (LN-prRLN) Metastasis.

Variables	LN-prRLN status		*p*
	Positive (n = 24)	Negative (n = 378)	
Age			
<55	14	220	.990
≥55	10	158	
Sex			
Male	13	78	<.001
Female	11	300	
Tumor size			
0-5.0 mm	5	187	.006
5.0-10.0 mm	19	191	
Coexistent Hashimoto's thyroiditis			
Yes	10	153	.908
No	14	225	
Tumor location			
Upper pole	3	114	.002
Middle third	3	119	
Lower pole	18	145	
Number of malignant foci			
1	21	330	1.000
2	3	48	
Capsular invasion			
No	19	319	.562
Yes	5	59	
LN-arRLN[a]			
No	0	317	<.001
Yes	24	61	
Lymphovascular invasion			
No	22	356	.646
Yes	2	22	
BRAF 600E mutation			
No	8	112	.701
Yes	16	266	

[a]LN-arRLN: lymph node anterior to the right recurrent laryngeal nerve.

these studies have shown that dissection of the LN-prRLN is required for tumors ≥10.0 mm in size, when there is cN+, and when there is extrathyroidal extension. However, the need for LN-prRLN dissection in patients with right lobe T1a PTC (when clinically observed) was not analyzed. Our study is the first to report the LN-prRLN metastasis rate for patients with T1a PTC of the right lobe (6.0%), which significantly increased when the PTC had a size of ≥5.0 mm and was located in the lower pole.

Tumor size was found to be an important prognostic factor in PTC. Dirikoc et al.[20] included 1184 patients with micro-PTC in their study and found that those with LN metastasis had significantly larger tumor sizes (≥5.75 mm) and primary tumor diameters (≥5.75 mm), which were predictive of LN metastasis (sensitivity, .782; specificity, .517). Goran et al.[21] investigated 257 patients with micro-PTC and reported that the LN metastasis rates significantly differed in terms of large (>5 mm) and small (≤5 mm) PTCs (46% and 24%, respectively). These findings indicated that a tumor >5 mm was related to an increased risk of LN-prRLN metastasis.

The effect of tumor location has also been analyzed in terms of LN metastasis. Tallini et al.[22] divided 298 patients with micro-PTC into four groups, according to: (i) the distance of the edge of the tumor from the thyroid capsule and (ii) tumor size. When the tumor size remained stable, the smaller the distance of the edge of the tumor from the thyroid capsule, the higher the possibility of LN metastasis. Wei et al.[23] investigated 710 patients with micro-PTCs; 276 patients had tumors in the lower pole, with an ipsilateral LN metastasis rate of 21.4%. This rate was lower than that reported in patients with tumors in the middle third (29.8%) and the upper pole (43.8%), suggesting a tendency for LN metastasis in cases of upper pole PTC. However, the authors did not clearly define these three locations nor distinguish between lateral and central LN metastases. Lateral LN metastasis could be promoted by tumors located in the upper third. Back et al.[24] noted that among 2967 patients with micro-PTC, patients with superiorly located PTC had a lateral LN metastasis rate of 16.2%, higher than that in patients with PTC at other locations (5.8%). Zheng et al.[25] investigated the effect of tumor location on central LN metastasis in 1587 patients with micro-PTC. In their study, the overall central LN metastasis rate was 30.9%, which increased to 31.0% when the tumors arose from the lower-third of the lobe and decreased to 23.1% when the tumor arose from the upper-third of the lobe. These differences were significant in the multivariate analysis. These findings support our results, which showed that a lower pole PTC was likely to develop LN-prRLN metastasis. In contrast, other similar studies have reported that tumor location did not affect LN-prRLN metastasis[10,18]; however, these studies performed a pooled analysis of patients with cN0, cN1a, and cN1b tumors. Therefore, we consider that the tumor location effect is likely to have been masked due to a clinically positive neck status.

The LN-prRLN metastasis pattern has been analyzed previously. Pinyi et al.[17] analyzed 405 patients with PTC and reported that, in most cases, LN-prRLN metastasis occurred after LN-arRLN metastasis. Only 6.4% of their patients showed isolated LN-prRLN metastasis. Chang et al.[19] reported that 148 patients had LN-prRLN metastases; however, only six patients were negative for LN-arRLN metastases. Lee et al.[14] found that, in their study, all 14 patients with metastatic disease in the LN-prRLN had a positive LN-arRLN, and that no patient had skip metastasis of the LN-prRLN. These findings are consistent with our results, suggesting that LN-prRLN dissection might not be required if there is no positive LN-arRLN.

The safety of LN-prRLN dissection is also an important issue. Theoretically, the RLN needs to be traced and elevated

Table 3. Multivariate Analysis of the Predictors of Lymph Node Posterior to the Right Recurrent Laryngeal Nerve Metastasis.

Variables	p	OR [95% CI]
Sex (male vs female)	.243	3.267 [.642-8.177]
Tumor size (5.0-10.0 mm vs 0-5.0 mm)	<.001	2.794 [1.265-6.558]
Tumor location (lower pole vs others)	<.001	2.007 [1.166-8.264]
LN-arRLN[a]	<.001	4.386 [1.932-10.556]

[a]LN-arRLN: lymph node anterior to the right recurrent laryngeal nerve.

during LN-prRLN dissection, as unintentional, excess pulling could cause nerve injuries. In a report by Zheng et al.[25] 1587 patients were divided into two groups based on the management of LN-prRLN dissection (yes or no). The complication rates of recurrent laryngeal nerve palsies, persistent hypocalcemia, chyle leakages, hematomas, and wound infections were similar between the two groups. Du et al.[6] and Chang et al.[19] described similar findings as those in our study, suggesting that the dissection of LN-prRLN was safe for patients.

Prophylactic central neck dissection in PTC cases remains controversial. Elective central neck dissection is considered useful in providing precise information concerning the disease stage, which is important when planning for radioiodine ablation intensity, and in avoiding a possible second surgery for residual metastatic lymph nodes.[26] Many studies have reported a <3.8% probability of regional recurrence despite an incidence of central LN metastasis ranging from 38% to 80%; however, no relationship has been found in terms of whether or not central neck dissection was implemented.[27] Two recent studies have reported that prophylactic central neck dissection significantly prevented regional nodal recurrence, but these studies reported no clear benefit in terms of long-term patient survival.[28,29] Geographical and genetic differences have been observed in PTC cases with LN metastasis.[30] Chinese patients were found to have more adverse pathologic features than western patients, and prophylactic central neck dissection was usually suggested for all patients with PTC in China.[31]

The limitations of the current study must be acknowledged. First, this was a retrospectively study, and there was inherent bias which may have affected the accuracy of our results. Second, sample size was not calculated before the study, and there might be other undetected independent predictors, more studies were required. Third, our finding was based on the data from a single medical center, so our findings need further validation before application.

Conclusion

In conclusion, LN-prRLN metastases is uncommon in patients with right lobe T1a PTC, but the possibility of their occurrence should not be overlooked when there are positive LN-arRLNs in patients with tumor size >5.0 mm, located in the lower pole. LN-prRLN dissection is recommended for these tumors.

Appendix

Abbreviations

AJCC	American Joint Committee on Cancer
ATA	American Thyroid Association
cN0	clinically negative central LN
CI	confidence interval
CTA	Chinese Thyroid Association
LN	lymph node
LN-arRLN	LN anterior to the right recurrent laryngeal nerve
LN-prRLN	LN posterior to the right recurrent laryngeal nerve
LVI	lymphovascular invasion
OR	odds ratio
PTC	papilliary thyroid carcinoma
RLN	right recurrent laryngeal nerve

Authors' Contributions

The conception and design of the work: HY, LT The collection and analysis of the data: HY, LT The interpretation of the statistic results: HY, LT Manuscript writing and revision: HY, LT All authors had approved the newest submitted version.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

Ethical Approval

Henan Cancer Hospital institutional research committee approved our study (LC20210533, May 5, 2021) and all participants signed an informed consent agreement for medical research before initial treatment. And all the related procedures were consistent with Ethics Committee regulations.

Data Availability

All data generated or analyzed during this study are included in this published article. And the primary data could be achieved from the corresponding author.

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