

ORIGINAL RESEARCH ARTICLE

Predictive factors of rVlb lymph node metastasis in papillary thyroid microcarcinoma

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Abstract

Introduction: Papillary thyroid microcarcinoma is common, but predictors of metastasis to the right recurrent laryngeal nerve deep lymph nodes (rVlb) are unclear.

Objective: To investigate the predictive factors of lymph node metastasis (LNM) in the rVlb of the right recurrent laryngeal nerve (rRLN) in papillary thyroid microcarcinoma (PTMC) patients, and to examine the correlation between rRLN superficial lymph node (rVla) and rVlb LNM in these patients.

Methods: Based on rVlb metastasis status, 772 PTMC patients admitted to our hospital from July 2013 to June 2016 were divided into two groups. χ^2 test and multivariate logistic regression were used to analyze the risk factors of rVlb metastasis.

Results: The rVlb metastasis rate was 7.1% (55/772). Univariate analysis showed that factors correlated with rVlb metastasis included gender, age, tumor size, tumor location, extrathyroidal invasion, metastasis in the left central area IVI + rVla, lateral lymph node metastasis (LLNM), concurrent nodular goiter, right tumor location, rVla LNM, and the number and ratio of metastatic lymph nodes. Multivariate analysis identified male sex, extrathyroidal invasion, rVla metastasis, LLNM, and right tumor location as independent predictive factors for rVlb.

Conclusion: Male sex, extrathyroidal invasion, rVla LNM, LLNM, and upper right tumor location were independent risk factors for rVlb metastasis. rVlb metastasis was positively correlated with the number and ratio of rVla metastatic lymph nodes. The risk of LNM in rVlb increased 8.4-fold when the number of metastatic lymph nodes was ≥ 2 (compared with <2 metastatic nodes) and 10.9-fold when the metastasis ratio of rVla nodes exceeded 60% (compared with $\leq 60\%$ metastatic ratio). Patients at high risk for rVlb metastasis should be considered for more comprehensive rVlb dissection, including central lymph node dissection.

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Keywords: Central lymph node dissection; Deep lymph nodes of recurrent laryngeal nerve; Papillary thyroid microcarcinoma; rVlb lymph node metastasis

1. Introduction

The World Health Organization defined papillary thyroid carcinoma of ≤ 1.0 cm as papillary thyroid microcarcinoma (PTMC),¹ which has accounted for 36–60% of newly diagnosed thyroid cancer in recent years.² According to Surveillance, Epidemiology, and End Results epidemiology data, the incidence of PTMC increased by an average

of 19.3% per year from 1983 to 2006,³ becoming the most common type of thyroid cancer in patients over 45 years of age.⁴ The cervical lymph node metastasis rate in PTMC patients ranges from 24.1 to 64.1%.⁵ In PTMC, central lymph node (CLN) recurrence and residual disease account for 80% of all recurrent cases.⁶ Notably, right recurrent laryngeal nerve (rRLN) deep lymph node (rVlb) recurrence accounts for 59% of CLN recurrence,⁷ making it the most common site of recurrence.⁸ Surgical dissection of rVlb as part of CLN significantly reduces the recurrence rate and the need for reoperation.⁹ Although several thyroid guidelines recommend including rVlb in central lymph node dissection (CLND) for patients with cervical lymph node metastasis (LNM),^{10–12} there is no consensus regarding the optimal individualized extent of CLND. Currently, all patients undergo the same extent of CLND regardless of their risk, which may be unnecessary or inappropriate.

On the right side of the trachea, aside from 0.21–1.6% of cases with nonrecurrent inferior laryngeal nerve,¹³ the space between the rRLN and esophagus is often filled with adipose tissue and lymph nodes. Surgery in the rVlb area carries a high risk of complications. Preoperative high-resolution ultrasound (US) and computed tomography have limited sensitivity (due to anatomical location) for detecting CLN metastasis in this region (only 23–38%).^{14–16} Incomplete dissection increases the risk of recurrence and complications associated with reoperation.^{17–19} Therefore, more reliable predictors of rVlb LNM are needed. Previous studies have indicated that tumor size > 1 cm is a risk factor of rVlb LNM in papillary thyroid carcinoma patients,^{20–22} but further research focusing specifically on PTMC cases is needed.

2. Materials and methods

2.1. Patients

Eligibility criteria included: initial thyroid surgery; no past history of head and neck surgery or radiation; no prior malignant tumors or other types of thyroid cancer; postoperative paraffin pathological diagnosis of PTMC, with clearly marked superficial and deep lymph nodes of the rRLN; complete medical records, surgical notes and US examination data; and surgical range including at least the right CLN.

A total of 772 PTMC patients who underwent initial surgery at the Thyroid Clinical Diagnosis and Treatment Center of the First Affiliated Hospital of Kunming Medical University from July 2013 to June 2016 were included. Of these, 656 cases underwent total/near-total thyroidectomy and 116 cases underwent ipsilateral + isthmus thyroidectomy; 673 received CLND and 99 received right

CLND; 67 underwent lateral compartment lymph node (LLN) modified radical neck dissection. The CLND range followed the revised cervical lymph nodes division of the American Society for Head and Neck Surgery (2002)²³ and the American Multidisciplinary Consensus (2009),²⁴ including all paratracheal, pretracheal, and prelaryngeal lymph nodes and associated adipose tissues. The internal edge of right CLND extended to the nourishing vein of lymph nodes above the contralateral thymus. All patients underwent prophylactic CLND. For total thyroidectomy or tumors in the right lobe, both superficial and deep rRLN lymph nodes were dissected. For convenience, left CLN, rRLN superficial, and deep lymph nodes were recorded as lVI, rVIa, and rVlb, respectively, with rVIa and rVlb boundaries defined by the level of the rRLN. This study was approved by the Ethics Committee of the First Affiliated Hospital of Kunming Medical University (No. 17-1 of ethical review L in 2017). All participants provided informed consent.

2.2. Indicators and measurement

Clinical data were collected for basic patient information. Tumor size, multifocality, extrathyroidal invasion, and concurrent thyroid disease were determined from reports completed by at least two experienced pathologists. For multifocal carcinomas, the largest nodule was measured; for irregular carcinomas, the longest cancer nodule was used. Tumors located in both bilateral lobes or unilateral lobe + isthmus were considered bilateral multifocal carcinoma. Tumor location was categorized as left, right, isthmus, or bilateral based on preoperative US examination and surgical records. Based on preoperative US localization, tumors in the right thyroid lobe were divided along their longitudinal axis into three equal parts: the upper (upper 1/3), middle (middle 1/3), and lower (lower 1/3) parts. The ratio of rVIa-positive lymph nodes to the total number of dissected lymph nodes was defined as the rVIa metastasis ratio. All operations were performed by experienced thyroid surgeons whose annual surgical loads were >100.²⁵

2.3. Statistics

Statistical analyses were performed using SPSS 20.0. The χ^2 test was used for categorical data. Two independent samples t-test and the two-sample rank-sum test for completely randomized designs were used for continuous data. Logistic regression analysis was performed for multivariate analysis. $p < 0.05$ was considered statistically significant.

3. Results

Among the 772 PTMC patients, the male-to-female ratio was 1:5, and the mean age was 43.93 ± 9.96 years. CLNM

occurred in 265 patients, and LLNM in 42, corresponding to metastasis rates of 34.3% and 5.4%, respectively. A total of 55 cases (7.1%) had rVIb metastasis. rVIb LNM was related to gender, age, tumor size, tumor location, extrathyroidal invasion, combined IVI + rVIa metastasis, rVIa metastasis, LLNM, and coexistence with nodular goiter ($p < 0.001$) (Table 1). The LNM rates in IVI, rVIa, and rVIb were 16.3% (126/772), 22.5% (174/772), and 7.1% (55/772), respectively. Among all cases with rVIb LNM, 4, 35, and 12 cases had concurrent IVI, rVIa, and LLN metastasis, respectively, while 16 cases (29.1%) had isolated rVIb metastasis.

The rVIb-positive tumors were predominantly located on the right side (67.3%). Therefore, the different regions of tumors in the right thyroid were divided into four subgroups (i.e. upper part, middle part, lower part, and multiple regions). The rVIb lymph node metastasis rates were highest in the upper part (12.3%), followed by the middle part (11.2%) and the lower part (6.4%), with the differences being statistically significant ($p = 0.014$) (Table 2).

Univariate analyses identified variables correlated with rVIb metastasis, which were further evaluated using logistic regression. As shown in Table 3, male sex, extrathyroidal invasion, rVIa metastasis, LLNM, and right tumor location were independent risk factors for rVIb metastasis.

Multivariate analysis showed that rVIa metastasis was an independent risk factor for rVIb metastasis. Further subgroup analysis was performed based on the number and ratio of rVIa metastatic lymph nodes. Using the rank-sum test for completely randomized two-sample data, both the number of and the ratio of rVIa metastatic lymph nodes were significantly associated with rVIb metastasis ($z = -8.060, p < 0.001$; $z = -8.479, p < 0.001$). When the number of rVIa metastatic lymph nodes was 0, 1, 2, and ≥ 3 , the corresponding rVIb metastasis rates were 3.3%, 12.4%, 25.6%, and 30.4%, respectively ($p < 0.001$). When the ratio of rVIa metastatic lymph nodes was 0, 1–20%, 21–40%, 41–60%, 61–80%, and 81–100%, the rVIb metastasis rates were 3.3%, 3.1%, 14.3%, 20.6%, 27.3%, and 43.3%, respectively ($p < 0.001$) (Table 4).

4. Discussion

This study provides evidence that rVIb lymph node metastasis is not a random event in PTMC but is significantly associated with specific clinicopathological factors and the metastatic burden within the rVIa compartment. Key predictors identified include male sex, extrathyroidal invasion, rVIa metastasis, LLNM, and right tumor location in the upper part of the lobe. Furthermore,

the number and ratio of metastatic lymph nodes in rVIa emerged as strong, clinically accessible intraoperative predictors, with a metastatic ratio exceeding 60% or the presence of ≥ 2 positive nodes substantially increasing the risk of rVIb involvement.

The surgical management of the rVIb region remains challenging due to its complex anatomy, which harbors the right recurrent laryngeal nerve, parathyroid glands, and their vascular supply. Consequently, this area is often under-dissected to avoid complications such as nerve injury and hypoparathyroidism. However, given that rVIb is reported to be the most common site of locoregional recurrence, accounting for up to 47.2% of central neck recurrences,^{6,7} an incomplete dissection may trade short-term safety for a higher long-term recurrence risk. Therefore, surgeons must carefully balance the risk of recurrence against surgical morbidity. Selective rVIb lymph node dissection can effectively reduce recurrence rates while minimizing operative risk for patients at low risk of metastasis. In a European quality-of-life study of thyroid cancer patients, recurrence emerged as the top concern (70.9%) among 25 common issues.²⁶ Similarly, a South Korean survey reported that 53% of patients prioritized lower recurrence risk even at the expense of higher complication rates.²⁷ These findings highlight the importance patients place on recurrence avoidance. Surgeons must therefore carefully weigh the risk of disease recurrence against the potential for surgical morbidity, especially when performing primary or reoperative central neck dissection in the anatomically constrained level rVIb region. This is to ensure that the treatment aligns with both patient preferences and oncologic goals.²⁸

While numerous studies have established that females aged ≥ 45 years have a higher incidence of PTC, male sex and younger age are recognized as independent predictors of LNM in general.^{5,29,30} Prior studies focusing specifically on rVIb LNM in PTC, however, reported no significant association with gender or age.^{20,21,31} In our cohort, both male sex and age < 45 years were associated with significantly higher rVIb metastasis rates ($p < 0.001$), with multivariate analysis confirming male sex as an independent risk factor for rVIb metastasis (odds ratio [OR] = 0.373, 95% confidence interval [CI]: 0.197–0.706). This discrepancy may reflect our exclusive focus on microcarcinomas (tumors ≤ 1 cm).

Regarding tumor location, rVIb metastasis rates were 9.8% for right-lobe tumors and 6.9% for bilateral tumors. No rVIb metastases occurred in the seven patients with isthmus tumors. Among 169 left-sided tumors, only three cases (1.8%) exhibited rVIb involvement. To minimize confounding, we analyzed 379 right-sided tumors stratified

Table 1. Clinical and pathologic features of patients with or without rVlb compartment metastasis

	Total <i>n</i> = 772	rVlb (+) <i>n</i> = 55	rVlb (–) <i>n</i> = 717	<i>p</i> -value
Gender				<0.001
Male	140 (18.1%)	21 (38.2%)	119 (16.6%)	
Female	632 (81.9%)	34 (61.8%)	598 (83.4%)	
Age				0.005
<45 years	420 (54.4%)	40 (72.7%)	380 (53.0%)	
≥45 years	352 (45.6%)	15 (27.3%)	337 (47.0%)	
Tumor size(cm)				
Mean ± SD		0.75 ± 0.26	0.62 ± 0.25	<0.001
≤0.5 cm	328 (42.5%)	15 (27.3%)	313 (43.7%)	0.018
0.5–1.0 cm	444 (57.5%)	40 (72.7%)	404 (56.3%)	
Tumor location				0.008
Left	169 (21.9%)	3 (5.4%)	166 (23.2%)	
Right	379 (49.1%)	37 (67.3%)	342 (47.7%)	
Isthmus	7 (0.9%)	0 (–)	7 (0.9%)	
Bilateral	217 (28.1%)	15 (27.3%)	202 (28.2%)	
Multifocality				0.881
Yes	288 (37.3%)	20 (36.4%)	268 (37.4%)	
No	484 (62.7%)	35 (63.6%)	449 (62.6%)	
Right multifocality				0.693
Yes	262 (33.9%)	20 (36.4%)	242 (33.8%)	
No	510 (66.1%)	35 (63.6%)	475 (66.2%)	
Extrathyroidal invasion				<0.001
Yes	44 (5.7%)	9 (16.4%)	35 (4.9%)	
No	728 (94.3%)	46 (83.6%)	682 (95.1%)	
IVI + rVIa metastasis				<0.001
Yes	249 (32.3%)	39 (70.9%)	210 (29.3%)	
No	523 (67.7%)	16 (29.1%)	507 (70.7%)	
rVIa metastasis				<0.001
Yes	174 (22.5%)	35 (63.6%)	139 (19.4%)	
No	598 (77.5%)	20 (36.4%)	578 (80.6%)	
LLNM				<0.001
Yes	42 (5.4%)	12 (21.8%)	30 (4.2%)	
No	730 (94.6%)	43 (78.2%)	687 (95.8%)	
Combined with Hashimoto's disease				0.971
Yes	279 (36.1%)	20 (36.4%)	259 (36.1%)	
No	493 (63.9%)	35 (63.6%)	458 (63.9%)	

(Cont'd...)

Table 1. (Continued)

	Total <i>n</i> = 772	rVIb (+) <i>n</i> = 55	rVIb (–) <i>n</i> = 717	<i>p</i> -value
Combined with nodular goiter				0.035
Yes	238 (30.8%)	10 (18.2%)	228 (31.8%)	
No	534 (69.2%)	45 (81.8%)	489 (68.2%)	

Abbreviations: IVI: Left central lymph nodes; LLNM: Lateral lymph node metastasis; rVIa: Right recurrent laryngeal nerve superficial lymph nodes; rVIb: Right recurrent laryngeal nerve deep lymph nodes.

Table 2. Correlation between tumors located in the right thyroid regions and rVIb metastasis

	Total <i>n</i> = 379	rVIb (+) <i>n</i> = 37	rVIb (–) <i>n</i> = 342	<i>p</i> -value
Tumor region ^a				0.014
Upper part	57 (15.0%)	7 (18.9%)	50 (14.6%)	
Middle part	215 (56.8%)	24 (64.9%)	191 (55.9%)	
Lower part	94 (24.8%)	6 (16.2%)	88 (25.7%)	
Multiple regions ^b	13 (3.4%)	0 (–)	13 (3.8%)	

Notes: ^a Tumors were located in different regions of the right thyroid. ^b In 13 cases of multifocal cancer, tumors occupied two or more regions. Abbreviation: rVIb: right recurrent laryngeal nerve deep lymph nodes.

Table 3. Multivariate logistic regression analysis of rVIb lymph node metastasis

Parameter	<i>p</i>	Exp (B)	95% CI for Exp (B)	
			Lower	Upper
Gender	0.002	0.373	0.197	0.706
Age	0.073	0.549	0.284	1.058
Tumor size	0.117	1.689	0.874	3.263
Tumor location	0.249	1.213	0.873	1.685
Extrathyroidal invasion	0.005	3.733	1.500	9.291
IVI + rVIa metastasis	0.488	1.524	0.464	5.011
rVIa metastasis	<0.001	4.556	2.447	8.483
LLNM	0.006	3.286	1.401	7.710
Combination with nodular goiter	0.324	0.682	0.319	1.460
Right tumor region	0.017	1.415	1.063	1.883
Constant	0.095	0.298		

Note: Exp (B): odds ratio.

Abbreviations: IVI: Left central lymph nodes; LLNM: Lateral lymph node metastasis; rVIa: Right recurrent laryngeal nerve superficial lymph nodes; rVIb: Right recurrent laryngeal nerve deep lymph nodes.

Table 4. Correlation between the number and ratio of rVIa metastatic lymph nodes and rVlb lymph node metastasis

	Total (n = 772)	rVlb (+) (n = 55)	rVlb (–) (n = 717)	p-value
Number of metastatic rVIa lymph nodes				
Median (IQR)		1.00 (0.00–3.00)	0.00 (0.00–0.00)	<0.001
0	598 (77.5%)	20 (36.4%)	578 (80.6%)	<0.001
1	89 (11.5%)	11 (20.0%)	78 (10.9%)	
2	39 (5.0%)	10 (18.1%)	29 (4.0%)	
≥3	46 (6.0%)	14 (25.5%)	32 (4.5%)	
Ratio of metastatic rVIa lymph nodes				
Median (IQR)		40% (0.00–0.80)	0.0% (0.00–0.00)	<0.001
0	598 (77.5%)	20 (36.4%)	578 (80.6%)	<0.001
1–20%	32 (4.1%)	1 (1.8%)	31 (4.3%)	
21–40%	56 (7.3%)	8 (14.6%)	48 (6.7%)	
41–60%	34 (4.4%)	7 (12.7%)	27 (3.8%)	
61–80%	22 (2.8%)	6 (10.9%)	16 (2.2%)	
81–100%	30 (3.9%)	13 (23.6%)	17 (2.4%)	

Abbreviations: rVIa: Right recurrent laryngeal nerve superficial lymph nodes; rVlb: right recurrent laryngeal nerve deep lymph nodes.

by lobe location, excluding bilateral disease to account for potential contralateral spread. Tumors in the upper third of the right lobe demonstrated the highest rVlb metastasis rate (OR = 1.415, 95% CI: 1.063–1.883), consistent with lymphatic drainage patterns in which the upper and middle thyroid regions preferentially drain to the rVlb compartment.³² This anatomical rationale also supports the observed propensity for “skip metastases” to lateral compartment level II from upper-pole tumors. Although our hypothesis was largely validated, the rare occurrence of rVlb metastasis from left-sided tumors (1.8%) remains partially unexplained. Similar low rates (1.3–3.8%) have been reported in prior studies,^{20,21,33} possibly reflecting secondary metastasis via the IVI. Although multifocality itself has not been linked to rVlb LNM, the impact of tumors occupying multiple sub-regions within a lobe warrants further investigation in larger cohorts.

Previous studies identified tumor size (≥1–2 cm) and extrathyroidal invasion as predictors of rVlb LNM in PTC,^{21,22,34} though the independent role of extrathyroidal invasion has been debated. Earlier series with limited PTMC samples reported rVlb metastasis rates ranging from 2.4% to 6.8%,^{20–22,32} similar to our overall rate of 7.1%. Tumors measuring 0.5–1.0 cm in our study showed a higher rVlb metastasis rate than those ≤0.5 cm (9.0% vs. 4.6%), but this difference was not statistically significant in

multivariate analysis ($p = 0.127$). In contrast, extrathyroidal invasion was a strong independent predictor, with an rVlb metastasis rate of 20.5% in the extrathyroidal invasion group versus 6.3% in the non-extrathyroidal invasion group (OR = 3.733, 95% CI: 1.500–9.291). This suggests that extrathyroidal invasion reflects a more invasive tumor phenotype, thereby supporting comprehensive surgical clearance of the rVlb region during CLND.

Both univariate and multivariate analyses confirmed significant associations between rVlb LNM and either rVIa LNM or LLNM. rVIa metastasis and LLNM were independent risk factors for rVlb involvement, consistent with Liu *et al.*²², whereas Zhang *et al.*²⁰ identified ≥3 LLNM as a predictive threshold. In this study, rVlb metastasis rates were 20.1% with rVIa metastasis and 28.6% with LLNM. Notably, when rVIa involvement reached ≥2 metastatic nodes or a metastatic ratio > 60%, rVlb metastasis rates increased sharply to 39.3% and 57.6%, respectively, representing 8.4-fold and 10.9-fold increases over rates observed in cases below these thresholds. These findings suggest that intraoperative frozen-section evaluation of rVIa lymph nodes, assessing both the number and ratio of metastases, could guide selective extension of dissection to rVlb, optimizing oncologic clearance while minimizing unnecessary dissection in this anatomically complex area.

Recurrence of rVlb lesions poses particular challenges

due to their propensity to invade critical adjacent structures and difficulty in timely detection, which may adversely affect tumor staging and long-term prognosis. Reoperation in this region is complicated by scar tissue adhesions, increasing surgical difficulty and, consequently, elevating the risk of complications, which may impose additional psychological, physical, and economic burdens on patients. Data from 2014 indicate that the average five-year survival rate for thyroid cancer in China was 67.5%, substantially lower than rates in Europe (86.5%) and the United States (98.2%).^{35–37} Recurrence and distant metastasis remain leading causes of mortality, largely attributable to variations in diagnostic and therapeutic standards. An urgent concern in China is the under-treatment of thyroid cancer, compounded by poor patient compliance, as evidenced by loss to long-term follow-up exceeding 40% in some cohorts and inconsistent adherence to postoperative US surveillance and thyroglobulin monitoring. Whether routine prophylactic central lymph node dissection improves long-term survival warrants further investigation through large-scale prospective studies.

This study has several limitations. First, as a retrospective, single-center analysis, selection bias is inherent and may not fully represent broader patient populations. Second, the absence of long-term follow-up data precludes assessment of the impact of rVlb dissection on recurrence-free survival, disease-specific survival, and long-term complication rates. Third, although tumor location was determined by preoperative US, some degree of subjective interpretation cannot be excluded. Fourth, the sample size for certain subgroups—such as tumors located in the isthmus or those with isolated rVlb metastasis—was limited, which may have reduced the statistical power of the corresponding analyses. Consequently, our findings primarily offer guidance for surgical planning and intraoperative decision-making regarding rVlb dissection in PTMC, rather than establishing definitive long-term therapeutic standards. Future prospective, multi-center studies with standardized surgical protocols and systematic follow-up are warranted to validate these predictors and clarify their effect on oncologic outcomes and quality of life.

5. Conclusion

In conclusion, this study identified male sex, extrathyroidal invasion, rVla metastasis, LLNM, and right upper-pole tumor location as independent risk factors for rVlb metastasis in PTMC. Notably, the risk of rVlb metastasis showed a positive correlation with both the number and ratio of metastatic lymph nodes in rVla, increasing 8.4-fold with ≥ 2 involved nodes and 10.9-fold when the

metastatic ratio exceeded 60%. These findings support a risk-stratified surgical approach: comprehensive central lymph node dissection, including the rVlb region, is warranted for high-risk patients to minimize recurrence, whereas limited dissection may be appropriate in low-risk patients to reduce operative morbidity.

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Conflict of interest

All authors declare no conflicts of interest. Shuyan Zhao, Xing Peng, Yuting Li, Wen Liu, and Weiha Cao.

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Ethics approval and consent to participate

This study was approved by the Ethics Committee of the First Affiliated Hospital of Kunming Medical University (No. 17-1 of ethical review L in 2017). All participants provided informed consent.

Consent for publication

All participants provided informed consent for publication of their findings in this study.

Availability of data

Not applicable.

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