

Risk factors for posterior to right recurrent laryngeal nerve lymph node metastasis in papillary thyroid carcinoma

De-Guang Zhang, MM, Li Gao, PhD, Yu-Wen Miao, MM, Gao-Fei He, MM, Lei Xie, PhD.

ABSTRACT

الأهداف: التعرف على العوامل الخطر لنقيلة العقدة اللمفاوية العصبية الحنجرية الخلفية اليمنى LNM- في سرطان الغدة الدرقية الحلمي.

الطريقة: أجريت دراسة رجعية على 389 مريض مصاب بسرطان الغدة الدرقية الحلمي الأولي خضعوا لاستئصال الفص أو استئصال الغدة الدرقية الكلي وتشريح المقصورة الكلي الأيمن أو الجانبي المركزي مع أو بدون تشريح الرقبة الجانبي وذلك خلال الفترة من يناير 2013م ومايو 2010م في قسم جراحة الرأس والعنق، معهد الجراحة لجامعة وتشجيانغ، وتشجيانغ، الصين. تم دراسة النتائج الإكلينيكية وعوامل الخطر النسبية ل PRRLN-LNM وتحليلها.

النتائج: أظهرت الدراسة وجود مقصوره مركزية LNM في 50.9% (198/389) و PRRLN-LNM في 12.6% (49/389) مريض بينما ظهر 3.1% (12/389) لديهم PRRLN-LNM فقط. أظهر التحليل المتعدد أن الأعمار الأقل من 35 وأقل، وتمدد خارج الدرقية ETE، ونقيلة العقدة اللمفاوية الموجودة في المقصورة الجانبية، وأمام الحنجرة، وأمام الرغامى، ومجاور الرغامى تعد عوامل مستقلة PRRLN-LNM.

الخاتمة: أظهرت الدراسة أن الأعمار من 35 عام وأقل، و ETE، ونقيلة العقدة اللمفاوية الموجودة في المقصورة الجانبية، وأمام الحنجرة، وأمام الرغامى، ومجاور الرغامى تعد عوامل مستقلة PRRLN-LN. لذلك، يجب إجراء تشريح مركزي أيمن شامل بشكل روتيني لهؤلاء المرضى.

Objectives: To identify the risk factors for posterior right recurrent laryngeal nerve lymph node metastasis (PRRLN-LNM) in papillary thyroid carcinoma (PTC).

Methods: We conducted a retrospective study of 389 patients with primary PTC who underwent right lobectomy or total thyroidectomy, and comprehensive right or bilateral central compartment dissection (CCD) with or without lateral neck dissection

(LND) between January 2010 and May 2013 at the Department of Head and Neck Surgery, Institute of Micro-Invasive Surgery of Zhejiang University, Zhejiang, China. The clinicopathological findings were investigated, and relative risk factors for PRRLN-LNM were analyzed.

Results: Central compartment LNM were present in 50.9% (198/389), and PRRLN-LNM were present in 12.6% (49/389) of patients, wherein 3.1% (12/389) had PRRLN-LNM only. A multivariate analysis revealed that younger age (≤ 35 years), extrathyroidal extension (ETE), lateral compartment LNM, prelaryngeal LNM, pretracheal, and right paratracheal LNM were independent predictors of PRRLN-LNM.

Conclusion: This study revealed that younger age (≤ 35 years), ETE, prelaryngeal LNM, lateral compartment LNM, and pretracheal and right paratracheal lymph nodes (anterior to the right recurrent laryngeal nerve [level VIa]), LNM were independent factors of PRRLN-LN (level VIb). Therefore, comprehensive right CCD should be routinely performed for such patients.

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From the Department of Head and Neck Surgery, Institute of Micro-Invasive Surgery of Zhejiang University, Sir Run Run Shaw Hospital, Medical School, Zhejiang University, Zhejiang, People's Republic of China.

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Address correspondence and reprint request to: Dr. Lei Xie, Department of Head and Neck Surgery, Institute of Micro-Invasive Surgery of Zhejiang University, Sir Run Run Shaw Hospital, Medical School, Zhejiang University, Zhejiang, People's Republic of China. E-mail: xielei0330@163.com

The incidence of papillary thyroid carcinoma (PTC) is rapidly increasing due to the widespread use of ultrasound (US) and US-guided fine-needle aspiration (FNA).¹ Although PTC has a relatively indolent course, it frequently metastasizes to the regional lymph nodes. The central compartment lymph nodes are most frequently involved and the reported incidence of lymph node metastasis (LNM) ranges from 40-60%.² Cervical LNM does not seem to affect survival adversely, but it is proved to correlate with the persistence and the recurrence of this malignant disease, and the local recurrence in the central compartment has been reported to increase the mortality rates.³ Central compartment lymph nodes include the prelaryngeal, pretracheal, and paratracheal nodes on both sides.⁴ On the right side, paratracheal lymph nodes are present anterior and posterior to the right recurrent laryngeal nerve (RLN) and because of the anatomical variation of the right side, for a right-side central compartment dissection (CCD) to be comprehensive dissected, the lymph nodes the posterior to right RLN should be routinely removed.⁵ The area of posterior to right recurrent laryngeal nerve lymph nodes (PRRLN-LN) was also called the right upper paraesophageal lymph nodes, or the right paraesophageal lymph nodes in some studies,⁶⁻⁸ including some lymph nodes that exist between the right RLN and the esophagus and/or the prevertebral fascial, and some lymph nodes that may be found behind the right common carotid due to the anatomic variation. Unfortunately, because of the narrow anatomic space and difficult dissection, these lymph nodes are sometimes overlooked during the right-side CCD. On literature review, we found only 5 related studies⁶⁻¹⁰ reporting the posterior to right recurrent laryngeal nerve lymph node metastasis (PRRLN-LNM), but the management of the PRRLN-LN remains unclear. The purpose of this study was to investigate the incidence and risk factors of PRRLN-LNM in PTC.

Methods. We retrospectively reviewed the medical records of 389 patients who underwent initial surgery for primary PTC between January 2010 and May 2013 at the Department of Head and Neck Surgery, Institute

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of Micro-Invasive Surgery of Zhejiang University, Sir Run Run Shaw Hospital, Medical School, Zhejiang University, Zhejiang, People's Republic of China. The patients included in the study met the following criteria: no previous thyroid surgery, right lobe or both (or bilateral) lobe PTC, and the availability of sufficient medical records to this study. Patients who underwent right CCD for recurrent PTC were excluded. The primary tumors located only in the left thyroid lobe or isthmus were also excluded from this study. Preoperative examinations consisted of preoperative thyroid function tests, thyroid gland and neck lymph node US, and CT was performed in large tumors to assess local invasion. Ultrasound-guided FNA was not performed routinely. All patients signed an informed consent. All procedures were performed by the same group of surgeons. Our institutional review board approved this study, and this study was carried out according to the Principles of the Helsinki Declaration.

Surgical treatment. Intraoperative frozen section biopsy (FSB) of the thyroid lesion was routinely performed during surgery to make a diagnosis. With a pathological confirmation of PTC, the ipsilateral CCD was performed during initial surgery. Based on US and FSB, 3 types of surgical procedure were performed: 1) right lobectomy with ipsilateral CCD was performed in patients with small (<1 cm), unifocal, intrathyroidal PTC, and the absence of clinically involved cervical LNM; 2) total thyroidectomy with right CCD was performed in patients with thyroid cancer >1 cm, multifocal in right thyroid lobe, extrathyroidal extension (ETE) or presence of clinically involved cervical LNM; 3) total thyroidectomy with bilateral CCD was performed in patients with bilateral PTC by FSB. Lateral neck dissection (LND) was performed if preoperative US was suspicious for lateral compartment LNM.

Lymph nodes compartments. The CCD specimen was divided into 3 or 4 nodal sites: pretracheal and right paratracheal lymph nodes (anterior to the right RLN (level VIa), PRRLN-LN (level VIb), prelaryngeal or Delphian lymph nodes, and left paratracheal lymph nodes (in bilateral PTC cases). The lateral neck lymph nodes were resected en bloc and assessed altogether as an entirety. All the paraffin biopsy examinations were undertaken by the senior pathologists in a standardized procedure.

Clinicopathological factors assessed. Preselected risk factors included: gender, age at diagnosis, tumor multifocality (ipsilateral and contralateral), largest tumor size, tumor location, ETE, clinical T and N stage,

thyroid function, number of total and positive lymph nodes. The PTC location was categorized as previously described: the upper third, the middle third, the lower third, multifocal in the right lobe, or multifocal in both lobes. All patients diagnosed as differentiated thyroid cancer were staged according to the fifth edition of American Joint Committee on Cancer/ Union Internationale Against Cancer tumor, node, metastases (TNM) staging criteria. Extrathyroidal extension was evaluated based on intraoperative findings or paraffin biopsy examination.

Statistical analysis. Statistical analysis was conducted by Statistical Analysis System, version 9.0 (SAS Inc., Cary, NC, USA). The results were expressed as mean±SD. Associations of variables with PRRLN-LNM were performed by univariate analysis, using the Pearson chi-square test or Fisher's exact test for categorical variables and independent t-test, or Mann-whitney U test for continuous variables. All significant factors in univariate analysis were incorporated into multivariate analysis. The odds ratio (OR) and the 95% confidential interval (CI) were calculated using logistic regression to identify the independent predictors. Statistical significance was defined as $p < 0.05$.

Results. A total of 389 patients with PTC initially treated at our hospital were included in this study. There were 297 women and 92 men, with a mean age of 43.7 ± 11.0 years (range from 19-77). Based on US and FSB, 3 types of surgical procedure were performed: 1) right lobectomy with ipsilateral CCD (n=152), 2) total thyroidectomy with right CCD (n=131), and 3) total thyroidectomy with bilateral CCD (n=106), and 27 patients underwent LND. Two hundred and eighty (72%) patients had tumors in the right lobe, while 109 (28%) had tumor in bilateral lobes. The solitary primary tumor was limited in the right lobe in 223 patients, of which 64 (28.7%) patients had in the upper third of the thyroid lobe, 117 (52.5%, 117/223) in the middle third, and 42 (18.8%, 42/223) in the lower third. Multifocal tumors were identified in 159 (40.9%, 159/389) patients. According to clinical regional lymph nodes classification, prophylactic lymph node dissection was performed in 231 (59.4%, 231/389) cases and therapeutic lymph node dissection in 158 (40.6%, 158/389) cases.

Pathological characteristics of resected LNM. We divided the patients into 2 groups: group A (49 cases) with level VIb LNM, and group B (340 cases) without level VIb LNM. During postoperative pathology analysis, the mean number of resected level

Table 1 - Number (mean±SD) of removed lymph nodes in 389 patients with papillary thyroid carcinoma.

Lymph nodes	Group A (n=49)	Group B (n=340)
Prelaryngeal	1.22±0.87	1.26±1.34
Level VIa metastasis	2.92±2.43	0.81±1.61
Level VIa	5.47±3.23	5.88±3.79
Level VIb	3.29±1.00	3.32±2.72
Lateral compartment	38.13±14.77	34.50±16.42

VIa was 5.83 ± 3.72 (range 0-20), level VIb 3.32 ± 2.57 (range 0-22), prelaryngeal lymph nodes 1.25 ± 1.29 (range 0-7), and lateral compartment lymph nodes 36.52 ± 15.33 (range 6-69). The number of the removed lymph nodes of prelaryngeal, level VIa, level VIa metastasis, level VIb, and lateral compartment are listed in Table 1. Although there was no significant difference between both groups in the removed number of level VIa ($p=0.468$), the number of metastatic lymph nodes in level VIa in group A was significantly higher than group B ($p=0.000$). The number of metastatic lymph nodes in level VIb was 1.73 ± 1.11 in group A. One hundred and ninety-eight (50.9%) patients had LNM in the central compartment, the level VIa was present in 140 (36%) and level VIb LNM in 49 (12.6%) patients. Prelaryngeal LNM was present in 39 (10%) patients and 9 patients without level VIa and/or level VIb LNM. Skip metastases, which indicate lateral LNM without central compartment LNM was found in one patient, or level VIb LNM without level VIa LNM in one and 12 patients.

Predictors of LNM of level VIb. Univariate analysis of the clinicopathological factors indicated that level VIb LNM was significantly associated with age, thyroid function, clinical N stage, clinical T stage, tumor size, ETE, prelaryngeal LNM, lateral compartments LNM, level VIa LNM. There was no correlation of gender, tumor focality and laterality, and solitary lesion location between the 2 groups. Furthermore, from all significant factors during univariate analysis, logistic regression analysis confirmed age ≤ 35 years, ETE, lateral compartments LNM, prelaryngeal LNM, and level VIa LNM as the independent risk factors of level VIb LNM (Tables 2 & 3).

Surgical complications. Among 389 patients, 10 cases had transient RLN injury and 2 cases of permanent RLN were observed. Thirty-one cases had transient hypoparathyroidism and no permanent hypoparathyroidism was observed. Horner syndrome was observed in 2 cases, one of which recovered 3 months later.

Table 2 - Univariate analysis of demographic and clinicopathologic factors for level VIb LNM 389 patients with papillary thyroid carcinoma.

Demographics	Group A (n=49)	Group B (n=340)	P-value
<i>Age (years; mean±SD)</i>	38.1±12.4	43.8±11.0	0.0008
≤35	24	89	0.0010
>35	25	251	
<i>Gender</i>			0.2199
Male	15	77	
Female	34	263	
<i>Thyroid function</i>			0.0104
Euthyroidism	44	332	
Hyperthyroidism	4	5	
Hypothyroidism	1	3	
<i>Clinical N stage</i>			0.0002
cN0	17	214	
cN1	32	126	
<i>Clinical T stage</i>			0.0002
T1	28	275	
T2	2	11	
T3	13	46	
T4	16	8	
<i>Tumor size (cm)</i>	1.36±0.72	0.79±0.61	<0.0025
>1cm	29	75	<0.001
≤1cm	20	265	
<i>Tumor focality</i>			0.7626
Unifocal	28	202	
Multifocal	21	138	
<i>Solitary lesion location</i>			0.4078
Upper third	6	58	
Middle third	18	99	
Lower third	4	38	
<i>Tumor laterality</i>			0.8925
Right lobe	35	246	
Both lobes	14	94	
<i>Extrathyroidal extension</i>			0.0001
Positive	18	50	
Negative	31	290	
<i>Prelaryngeal LNM</i>			<0.0001
Positive	17	22	
Negative	32	318	
<i>Level VIa LNM</i>			<0.0001
Positive	37	103	
Negative	12	237	
<i>Lateral compartments LNM</i>			<0.0001
Positive	15	12	
Negative	34	328	

LNM - lymph node metastasis

Discussion. The benefit and appropriate extent of CCD in PTC patients remains controversial.¹¹ Some studies suggested that CCD performed routinely could decrease the recurrence of PTC and improve survival.^{12,13} However, when the CCD was performed the complications of surely be increased. Furthermore, the potential benefits of CCD should be weighed

Table 3 - Multivariate analysis for factors predicting level VIb LNM 389 patients with papillary thyroid carcinoma.

Variables	OR (95% CI)	P-value
Age ≤35	0.170-0.722	0.0045
ETE	1.233-5.935	0.0130
Level VIa LNM	1.256-6.115	0.0116
Prelaryngeal LNM	1.893-10.470	0.0006
Lateral compartments LNM	2.489-16.675	0.0001
Thyroid function	-	0.3312
Clinical N stage	-	0.7998
Clinical T stage	-	0.9758
Tumor size	-	0.0762

ETE - extrathyroidal extension, LNM - lymph node metastasis, OR - odds ratio, CI - confidential interval

against the associated complications, such as RLN injury and hypoparathyroidism. In this study, routine ipsilateral CCD was been performed as the treatment for PTC. Central compartment LNM was present in 50.9% (198/389) of patients, and PRRLN-LNM was present in 12.6% (49/389), including 3.1% (12 of 389) who had PRRLN-LNM only. A univariate analysis revealed that age, thyroid function, clinical N stage, clinical T stage, tumor size, ETE, prelaryngeal LNM, lateral compartments LNM, and level VIa LNM were risk factors for level VIb LNM. Multivariate analysis revealed that younger age (≤35 years), ETE, prelaryngeal LNM, lateral compartments LNM, and level VIa LNM were significantly correlated with level VIb LNM. Age is a known important risk factor of LNM in patients with PTC. Young ages (≤45 years) were associated with an increased risk of central compartment LNM, which was reported by several previous study.^{14,15} However, no significant association was found between level VIb LNM and age in previous studies.⁶⁻¹⁰ In this study, we found younger age (≤35 years) was associated with an increased risk of level VIb LNM during the univariate and multivariate analysis. These results indicate that the younger PTC patients (≤35 years) have stronger metastasis capacity in level VIb and level VIb dissection should be performed routinely in these patients.

Extrathyroidal extension is an indicator of a tumor's aggressive capacity, the incidence of ETE in well-differentiated thyroid cancer varies in previous reports, ranging from 5-34%.¹⁶ Some reports have shown that PTC patients with ETE had significant correlation with the central compartment and level VIb LNM.⁶⁻¹⁰ Corresponding with previous studies, 17.5% (68/389) of patients were found to have ETE of primary tumors in this study, including micro-spread out of the capsule and gross invasion, and the incidence of ETE was significantly higher in patients with level VIb LNM than those without level VIb LNM (36.7% versus 14.7%, *p*<0.05). Previous reports^{6-8,10}

suggested that level VIb LNM was associated with level VIa (pre- and paratracheal lymph nodes) and lateral compartments LNM. However, in those studies, the prelaryngeal or Delphian lymph nodes were both included in the paratracheal lymph nodes. Unlike previous studies, the prelaryngeal or delphian lymph nodes were classified as an independent compartment in our study, the univariate and multivariate analysis both demonstrated that level VIb LNM was not only significantly associated with nodal involvement in level VIa and lateral compartments LNM, but also with prelaryngeal compartments LNM. Thus, we conclude that the PTC patients with level VIb LNM may have strong metastatic capacity and have multiple channels of lymphatic system metastatic potentiality. In addition, similar to previous reports,^{6,8} the number of metastatic lymph nodes in level VIa in group A was significantly higher than that in the group B ($p=0.000$). According to the outcome of the univariate analysis, we found that level VIb LNM was significantly associated with the tumor size, which corresponded with previous studies on level VIb LNM.⁶⁻¹⁰ However, unlike the previous reports, when the tumor size was adjusted with other factors, in the multivariate analysis, the tumor size was not an independent risk factor for the level VIb LNM. Because factors such as level VIa, prelaryngeal and lateral compartments LNM might limit the statistic power of this result, it was possible that level VIb LNM was associated with tumor size. In our department, we performed a routine ipsilateral CCD for patients with PTC regardless of the tumor size.

Unlike previous reports,^{6,10} we found no correlation between tumor multifocality and level VIb LNM. Tumor multifocality was originally considered to be an expression of intrathyroidal metastases and recognized as a risk factor. However, some authors¹⁷ found that thyroidal tumor foci have different gene rearrangement, which suggests that they may arise as distinct cancers. Thus, the presence of multifocality may not indicate increasing metastasis potentiality.

Study limitations. Tumors only involving the left lobe or isthmus was excluded in this study and this might cause selective bias. Our clinical study is a single-center design, unable to include all risk factors, some of which may be critical for predictors. In addition, due to the short term follow-up, we cannot evaluate the locoregional recurrence, distant metastasis, and prognosis of the level VIb dissection. Further research will focus on long term follow-up outcomes. Meanwhile, we recommend a well designed prospective

randomized controlled study that considers level VIb dissection related morbidity, locoregional recurrence, and distant metastasis.

In conclusion, this study revealed that younger age (≤ 35 years), ETE, prelaryngeal LNM, lateral compartments LNM, and level VIa LNM were independent factors of level VIb LNM. Therefore, comprehensive right CCD should be routinely performed for such patients. We recommend multicenter research and long term follow-up to better understand the risk factors and surgical management of PTC.

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