Analysis of risk factors for posterior laryngeal recurrent nerve metastasis in micropapillary thyroid carcinoma

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Abstract. Posterior recurrent laryngeal nerve (RLN) lymph node dissection remains controversial in the operation of thyroid cancer, especially in cases of papillary thyroid microcarcinoma (PTMC). The present study aimed to evaluate the risk factors for posterior RLN lymph node metastasis in patients with PTMC. Two hundred and thirty-nine patients pathologically diagnosed with PTMC after surgery between June 2016 and June 2017 were included. Risk factors including age, sex, tumor diameter, multiple tumor focus, membrane invasion and lateral cervical lymph node metastasis condition, were analyzed, and their corresponding OR values were calculated. The results indicated that posterior RLN lymph node metastasis was pathologically identified in 27/239 patients. Membrane invasion ($p = 0.024$), VIa lymph node metastasis ($p < 0.01$), and lateral cervical lymph node metastasis ($p < 0.01$) were considered to be risk factors for posterior RLN lymph node metastasis. It is concluded that membrane invasion, VIa lymph node metastasis, and lateral cervical lymph node metastasis significantly increased the incidence of posterior RLN lymph node metastasis. Complete dissection of the posterior RLN lymph node was essential for patients with these risk factors.

Key words: Thyroid cancer, Posterior recurrent laryngeal nerve metastasis, Thyroidectomy

THE INCIDENCE of thyroid cancer has increased rapidly in recent decades worldwide [1, 2]. Papillary thyroid carcinoma (PTC) accounts for approximately 90% of thyroid carcinomas. It is referred to as papillary thyroid microcarcinoma (PTMC) when the maximum PTC diameter is less than 1 cm [3].

PTMC has the same malignant biological characteristics as PTC, which also invades the thyroid capsule and surrounding tissues, and is prone to developing into central lymph node metastasis (CLNM) or even distant metastasis [4]. Therefore, the method to correctly treat PTMC has become an urgent clinical problem. In recent years, surgical treatment of PTC has gradually reached a consensus, but avoiding the dissection of CLNM during PTMC surgery remains controversial. The thoroughness, safety and feasibility of CLNM dissection influence the outcome and complications of thyroid cancer treatment.

VI lymph node region was defined as inferior internal jugular node or pretracheal lymph nodes according to the AJCC lymph node classification. The recurrent laryngeal nerve (RLN) abuts the central tracheal esophageal sulcus lymph node, which divides the VI lymph node region into shallow (VIa) and deep (VIb) subregions [5]. Dissection of the lymph node posterior to the right RLN (LN-prRLN) is sometimes not performed in a large portion of PTMC surgery cases to reduce the risk of RLN and parathyroid injury, such that the adipose tissue of the CLN is usually not completely removed. In our study, we used RLN and its branches as the boundary to clean the VIa and VIb layers of the right central region in PTMC patients. The VIa and VIb lymph node regions were each managed. The incidence of VIb metastasis rate and related clinical characteristics in patients with PTMC were investigated by postoperative paraffin pathology. Our study aimed to investigate the risk factors for VIb metastasis and the feasibility of completing VIb dissection to avoid the possibility of the lymph node residual metastasis. This study was conducted due to the concern of the incidence of complications among right thyroid cancer patients.

Materials and Methods

Patients

A total of 239 patients with PTMC who underwent
operation in Head and Neck department, Fujian Cancer Hospital and Fujian Medical University Cancer Hospital department from June 2016 to June 2017 were enrolled. The ethical approval was obtained from institutional review board of Fujian Medical Foundation. The surgeries were performed by a single surgeon in our department. The inclusion criteria were as follows: (1) Right thyroid gland cancer or bilateral thyroid nodule with right thyroid cancer; (2) Confirmation of PTMC via pathology after surgery; (3) An absence of previous history of thyroid surgery. The exclusion criteria were as follows: (1) Multifocal tumors with a maximum diameter >1 cm; (2) Thyroid malignant tumors with other pathological types; (3) Secondary malignant tumors in the thyroid; (4) Loss to follow-up after surgery. Preoperative thyroid and cervical lymph node ultrasound and CT were evaluated with reference to Kowalski’s cervical lymphography imaging criteria to determine the clinical lymph node metastasis stage before surgery [6].

Surgical procedure

The specific thyroidectomy procedure is not presented here. A complicated dissection of the VI lymph region was performed. To explore metastasis of the posterior RLN lymph node region (LN-prRLN alone), the right central region was divided into VIa and VIb subregions, with the RLN and its branch plane as the boundary. The VIa subregion lymph nodes include the cricothyroid membrane and the pretracheal and perithyroid lymph nodes. The VIb region, located posterior to the RLN, is attached to the esophageal surface. After lobectomy, the thymus tissue was routinely explored for the possibility of parathyroid presence. If the parathyroid gland was found inside the thymus, the thymus would be preserved in the operation. Then, the medial border was isolated along the boundary of the trachea, starting from the anterior tracheal tissue from the suprasternal fossa along the tracheal wall to the intercross between inferior thyroid artery and RLN. Subsequently, we reversed downward from the inner edge of the cervical vascular sheath separating the lateral boundary until we reached the deep innominate artery surface. After detaching the surrounding superficial lymph nodes, the tissues were carefully separated and removed from the deep RLN. The specimens were labeled as belonging to the VIa subregion (Fig. 1a). Thereafter, along the nerve, the RLN was completely dissected to detach it from the deep tissue. Then, the deep tissue was removed along the superior surface of the esophagus, up to the inferior thyroid artery, the medial border of the esophagus, the lateral border to the deep part of the common carotid artery, and down to the innominate artery. This tissue was labeled as belonging to the VIb subregion (Fig. 1b). In this process, the natural anatomical position of the RLN was maintained to avoid pulling, and the lower parathyroid gland which cannot be retained in situ during the CLND process, was immediately transplanted to the ipsilateral upper arm or sternocleidomastoid.

Postoperative histopathological examination

Thyroid tissue specimens were used to diagnose PTMC after the operation, and lymph node specimens labeled as belonging to the VIa or VIb subregions were sent for examination. If a patient underwent lateral cervical dissection, the II, III, IV, and V cervical lymph region tissues would be collected to identify the lymph nodes in each region.

Statistical analysis

Statistical analysis was conducted using SPSS software, version 24.0. All values were presented as means ± SDs. Differences between the different groups were

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**Fig. 1** Right central lymph node dissection via endoscopy (A) RLN exposed (B) Parathyroid in situ protection.
assessed using $t$-tests. Qualitative clinical characteristics were analyzed by $\chi^2$ test. Statistical significance was indicated by $p < 0.05$.

**Results**

**Clinical data**

A total of 239 patients (59 males) were included during the study period. The average age was 46.72 ± 8.35 years (range, 21–79 years). All patients underwent ipsilateral right lobectomy and ipsilateral CLND. Eighty-three patients had nodules limited to the right lobes, and bilateral glandular lobes were involved in 156 patients. All the patients received a preoperative ultrasound and enhanced cervical CT scan. Any highly suspected lymph node metastasis found before surgery was identified as clinically node-positive (cN1) stage. Overall, there were 63, 78 and 66, respectively. Additionally, 32 patients with cN1 underwent selective cervical lymph node dissection (LLND) concurrent treatment. Among the 207 cN0 patients, the number of patients who underwent unilateral thyroidectomy (uT) + rCND, total thyroidectomy (TT) + bilateral CND (bCND) were 63, 78 and 66, respectively. Additionally, 32 patients with cN1 underwent selective cervical lymph node dissection (LLND), total thyroidectomy (TT) + rCND, and TT + bilateral CND (bCND) were 63, 78 and 66, respectively. Among the 32 patients, 6 patients underwent uT + rCND + LLND, 9 patients underwent TT + rCND + LLND, 16 patients underwent TT + bilateral CND (bCND) + LLND, and 1 patient underwent TT + bCND + bilateral LND (bLND) (Table 1).

| Table 1 | Clinical Characteristics |
|---------|--------------------------|
|         | Included patient (N = 239) | Ratio (%) |
| Age (years) | 46.72 ± 8.35 | |
| Sex | | |
| male | 59 | 24.69 |
| Female | 180 | 75.31 |
| LND | | |
| Right | 83 | 34.73 |
| Bilateral | 156 | 65.27 |
| Operation (N = 329) | | |
| T + rCND | 63 | 23.36 |
| TT + rCND | 78 | 32.63 |
| TT + bCND | 66 | 27.61 |
| T + rCND + LLND | 6 | 2.51 |
| TT + rCND + LLND | 9 | 3.74 |
| TT + bCND + LLND | 16 | 6.69 |
| TT + bCND + LND | 1 | 0.42 |

**Postoperative pathology analysis**

According to the intraoperative frozen section pathology and postoperative routine pathology, the TNM staging was classified based on the 8th edition of the American Joint Committee on Cancer (AJCC) criteria published in 2017. Two hundred and thirty-nine patients were diagnosed with PTMC, of which 161 were in stage T1, 67 were in stage T3b and 11 were in stage T4a. Lymph nodes were also collected for pathological examination. Patients with stage N0, N1a and N1b were 112, 99 and 28, respectively. There were 113 patients with a tumor diameter larger than 5 mm and 126 patients with a tumor diameter smaller than 5 mm. Multiple lesions, including other benign tumors, were found in 118 patients. Membrane invasion was observed in 78 patients, of which 62 patients exhibited invasion of the anterior strap muscles. RLN invasion was found in 8 patients. The tumor was carefully isolated to RLN, and all invaded RLN nerves were preserved during surgery. There were 110 (46.03%) cases of lymph node metastasis in the VI region. Among them, VIa lymph node positivity was found in 73 (30.54%) patients, and VIb area metastasis in 9 (3.77%) patients. Coexisting VIa and VIb metastases was found in 18 (7.53%) patients. Among the 207 cN0 PTMC patients before operation, 79/207 (38.16%) patients had lymph node metastasis in VI, 71/207 (34.30%) patients were VIa positive, and 19/207 (9.18%) patients were VIb positive. There were 11/207 (5.31%) cases of lymph node metastasis in the VIa + VIb area, and only 9 cases (9/207, 3.87%) of lymph node metastasis in the VIb area. In 32 patients with cN1 PTMC, 28/32 (87.5%) had lateral neck metastasis, 21/32 (65.63%) had lymph node metastasis in the VI area, 20/32 (62.50%) had metastasis in the VIa area, 8/32 (25.00%) had metastasis in the VIb area, 7/32 (21.88%) had lymph node metastasis in the VIa + VIb area, and only 1/32 (3.13%) had metastasis along the VIb area. (Table 2)

**Risk factors associated with VIb subregion lymph node metastasis.**

Univariate analysis showed that age >55 years ($p = 0.950$), sex ($p = 0.269$), tumor diameter ($p = 0.083$), and multifocality ($p = 0.05$) were not significantly associated with VIb subregion lymph node metastasis ($p = 0.056$), while tumor invasion capsule ($p = 0.024$) and lymph node metastasis in the VIa subregion ($p < 0.001$) were correlated with lymph node metastasis in the VIb subregion. Cervical lymph node metastasis ($p = 0.002$) was related to lymph node metastasis in the VIb subregion (Table 3). According to multivariate analysis, tumor membrane invasion (OR = 3.872) and lymph node metastasis in the VIa subregion (OR = 7.138) were
independent factors affecting lymph node metastasis in the VIb subregion of PTMC patients (all $p < 0.05$, Table 4).

### Postoperative complications and recurrence

None of the patients suffered from postoperative bleeding or secondary surgery. Seventy out of the 170 (41.1%) patients undergoing total thyroidectomy had temporary hypoparathyroidism 24 h after the operation. Parathyroid hormone (PTH) level in all the patients returned to normal 7 to 14 days later. Ten patients suffered from temporary RLN injury, and all the patients suffered from RLN tumor invasion, in which RLN was physically isolated from the malignant tumor. In this condition, the nerve contusion was inevitably caused during operation. After postoperative voice training, all patients’ voices returned to normal in 1–6 months. During the two-year follow-up, the local recurrence rate was 0.8% (2/239). Both of patients with local recurrence did not receive LLND and had recurrence in the lateral cervical lymph region, which may be related to insufficient preoperative evaluation. No distant metastasis or death was observed in our study.

### Discussion

Traditionally, PTMC belongs to the indolent carcinomas, with growth rates of tumors over 3 mm of 5% and 8% in 5 and 10 years, respectively [7]. In a long-term study, the 10- and 15-year overall survival rates were 94.6% and 90.7%, respectively [8]. Generally, tumor size is unsuitable to serve as the only standard for evaluating tumor progression. A large number of PTMC patients did not belong to the early phase tumor group. Our study evaluated the TNM staging of differentiated thyroid cancer (DTC) in our center in accordance with the 8th AJCC guidelines (2017). A total of 78 patients (32.64%) were identified as T3b and T4a in the primary tumor evaluation. VI region lymph node metastasis was found in 110 patients (46.03%) with postoperative pathology identification. Although cN0 patients accounted for 86.61%
In our study, 239 patients with PTMC were included. Twenty-seven (11.30%) cases were identified with VIb subregion lymph node metastasis, which showed a similar LN-prRLN transfer rate among PTC patients. Thus, routine LN-prRLN cleaning seems necessary for PTMC treatment. Incomplete LN-prRLN dissection may increase the recurrence in local lymph nodes. If recurrence occurs, secondary surgery will cause significant scarring and increase the probability of damaging the RLN and parathyroid gland due to severe tissue adhesion [14].

We found that there was no significant correlation between VIb regional lymph node metastasis and the age, sex, tumor diameter and multifocal lymph node metastasis of PTMC patients, suggesting that the occurrence of VIb subregional metastasis in PTMC patients cannot be evaluated based only on clinicopathological characteristics. Therefore, the dissection of LN-prRLN is usually ignored.

In our study, 14 patients with PTMC had invaded capsules, which developed into VIb subregional lymph node metastasis. Further, the LN-prRLN metastasis rate in the invasion group (17.95%) was significantly higher than that of the noninvasion group (8.07%). Additionally, membrane invasion was identified as one of the independent risk factors in the multivariate analysis. These results are consistent with those of Luo et al. regarding PTC [12]. The probability of VIb subregional lymph node metastasis in patients with VIa subregional lymph node metastasis (19.78%, 18/91) was significantly higher than that among those without VIa subregional lymph node metastasis (6.08%, 9/148). VIa subregional lymph node metastasis was found to be an independent risk factor for VIb metastasis. In this study, there were 9 patients with no metastasis in the VIa subregion and only VIb subregion metastasis. Among these patients, 8 were in cN0 stage and 1 patient was in cN1 stage, indicating that PTMC can be independently transferred to the deep paratracheal RLN lymph nodes without invasion of the superficial lymph nodes. Therefore, LN-prRLN metastasis, especially LN-prRLN metastasis alone, is more worthy of attention. PTMC patients with cN0 or cN1 stage should be highly vigilant to avoid residual metastatic lymph nodes during operation. In addition, among 32 cN1 patients, lateral cervical neck lymph node metastasis was found in 28 patients. In this group, 8 patients (28.57%) were accompanied by VIb subregion metastasis. The metastasis rate was obviously higher than that of patients with no lateral cervical metastasis. Although the p value >0.05, the OR was 3.232 in the lateral cervical lymph node metastasis group. The authors believed that with further in-depth study with a larger sample, these factors will provide more references and guidance for a standard lymph node dissection strategy for the right central lymph node region.

According to the AJCC DTC guidelines on TNM staging and recurrence risk identification, as well as our clinical results, for cN0 right PTMC patients, only thyroidectomy and superficial lymph node resection performed in the right central region will result in the absence of metastatic lymph nodes in the VIb region dissection, which may lead to a low stratification of TNM staging. Therefore, the dissection of LN-prRLN is usually ignored.
staging and increase the risk of recurrence. Among the 239 PTMC patients in this group, preoperative ultrasound indicated that central lymph metastasis was found in only 17 cases (7.11%), and postoperative lymph metastasis was found in 110 patients (46.03%). Among 207 patients with cN0 PTMC, 79 patients had metastasis in the VI region and 19 patients had metastasis in the Vlb region. Among the Vlb region metastasis patients, 8 had only separate LN-prRLN metastasis.

It can be seen that standard and complete right CLND makes postoperative pathological staging and risk evaluation more accurate, especially for LN-prRLN metastasis-only patients. Huang et al. [15] retrospectively analyzed the pathological data of 136 patients with PTC with cN0 treated with LND preventive dissection. The results indicated that lymph node integrity dissection was conducive for definite TNM staging and recurrence risk stratification, which was consistent with the data in our study. In addition, Ducoudray et al. [16] followed up 603 PTC patients for 4.3 years after surgery. Their results showed that the recurrence rate was increased with TNM classification variation (2% recurrence in N0, 5% recurrence in N1a and 22% recurrence in N1b patients). Therefore, standardized and complete CLND not only reduces the risk stratification of cancer lesion residue and tumor recurrence but also contributes to scientific and accurate postoperative tumor staging. More importantly, complete Vlb lymph node isolation also contributes to individualized postoperation follow-up treatment.

LN–prRLN was closely associated with RLN. The cleaning process requires the entire process of RLN isolation, and hence the process will inevitably damage the fine branch of the RLN. Serpell et al. [17] reported that 50% to 60% of patients with laryngeal recurrent nerve have small branches into the trachea (sensory nerves), esophagus (sensory and motor nerves) and laryngopharyngeus (sensory and motor nerves). Twenty percent to 30% of RLN branches may dominate laryngeal movement, and electrical stimulation will cause electrical and mechanical movement in the throat. Therefore, careful LN-prRLN dissection to protect the RLN and related branches plays an important role in right thyroid cancer surgery.

In conclusion, our study found that the positive tumor membranes and Vla subregion lymph nodes were independent risk factors for LN-prRLN metastasis in PTMC patients. In the presence of these features, complete resection of the ln-prRLN risk seems to be the radical resection strategy for PTMC. Following this guidance, a reduced likelihood of local recurrence of the tumor may be achieved, which would be beneficial to the treatment of PTMC.

Acknowledgments

No acknowledgments.

Funding

This study received no funding.

Disclosure of Potential Conflicts of Interest

The authors declare that they have no conflict of interest.

Ethical Approval

Approval was obtained from the ethics committee of Fujian Medical University Cancer Hospital. The procedures used in this study adhere to the tenets of the Declaration of Helsinki.

Informed Consent

All participants provided their written informed consent.

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