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Risk Factors for Bilateral Lateral Lymph Node Metastasis in Unilateral Papillary Thyroid Cancer

Jee Won Moon, Yongmin Cho, Kyoung Ho Oh, Jae-Gu Cho, Seung-Kuk Baek, Soon Young Kwon, Kwang-Yoon Jung, Jeong-Soo Woo

Department of Otorhinolaryngology, Head and Neck Surgery, Korea University College of Medicine, Seoul, Korea

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ABSTRACT

Objective: This study investigated the factors associated with bilateral lateral lymph node (LN) metastasis in patients with unilateral papillary thyroid cancer.

Methods: The records of the patients who underwent total thyroidectomy with bilateral lateral neck dissection from 2009 to 2020 were investigated. Clinicopathologic characteristics of eligible patients were examined.

Results: Of 11 eligible patients, 72.8% had the primary tumor larger than 2 cm (18.2% larger than 4 cm), and central compartment metastasis was present in all patients at the time of the surgery. On the other hand, aggressive subtype, extranodal extension, and lymphovascular and perineural invasion were not identified in most of the patients. Furthermore, preoperative sonography detected all possible contralateral LN metastasis, while computed tomography missed contralateral metastasis in 1 patient.

Conclusion: A meticulous evaluation for contralateral LN metastasis using sonography is needed in unilateral papillary thyroid cancer patients with high risk factors.

Keywords: Lymph node dissection, metastasis, neck dissection, papillary thyroid cancer, thyroid

Introduction

Although papillary thyroid cancer (PTC) shows an excellent 5-year survival rate of up to 92.8%, it commonly metastasizes through lymphatic spread and the extent of lymph node (LN) involvement is one of the important prognostic factors for PTC.[1-3] Cervical level VI is most frequently involved in PTC, followed by lateral LNs with a high rate of occult metastasis, and the 2015 American Thyroid Association guideline stated that the completeness of surgical resection is an important determinant of outcome, recommending compartmental node dissection for those with clinically evident nodal disease.[4-6] Unilateral PTC mostly metastasizes to ipsilateral LNs, and patients with bilobar involvement, isthmic tumors, male sex, or extrathyroidal extension (ETE) are at a higher risk of bilateral cervical LN metastasis.[7,8] Meanwhile, there are some rare cases in which unilateral PTC presents with bilateral lateral LN involvement without evidence of bilobar disease. Since lateral neck metastasis is significantly related to disease persistence and locoregional recurrence, it is important not to miss the possible contralateral lateral LN involvement even in unilateral PTCs. Therefore, we investigated the factors associated with bilateral lateral lymph node metastasis in patients with PTC confined to the unilateral lobe with review of the literature.

Methods

Patient Selection

We retrospectively reviewed the medical records of the patients who underwent total thyroidectomy with bilateral selective neck dissection for thyroid cancer from 3 different tertiary hospitals from January 1, 2009 to December 31, 2020. We also looked into the patients who had a primary total thyroidectomy with or without neck dissection and later underwent subsequent neck dissection from our hospitals during follow-up. The inclusion criteria are as follows: (i) lymph node dissection for lateral neck compartments in both sides (at least one of the level II-V from each side) and (ii) histopathologic confirmation of unilateral thyroid cancer with bilateral metastatic lateral neck nodes. The exclusion criteria are as follows: (i) thyroid malignancies other than PTC, (ii) bilateral or isthmus PTC, (iii) previous history of radiotherapy or previous thyroid

Corresponding Author: Jeong-Soo Woo, e-mail: diakonos@korea.ac.kr
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surgery from other hospitals, and (iv) presence of distant metastasis.

For the preoperative evaluation, all patients underwent neck computed tomography and/or ultrasonography (US) to assess the primary tumor and nodal involvement. When needed, fine-needle aspiration was done for the suspicious lymph nodes to determine the extent of surgery. This study was approved by Ethics Committee of Korea University Guro Hospital (Approval No: 2022GR0257, Date: 23.06.2022), and informed consent was waived because of the retrospective nature of the study and the analysis used anonymous clinical data.

Pathology

The following information was obtained from the pathology reports: laterality of the tumor, tumor size (largest diameter), tumor multiplicity, extent of tumor (extrathyroidal extension), presence of lymphovascular or perineural invasion, extranodal extension, other thyroid pathology, and the number of harvested and metastatic lymph nodes from each anatomic neck level. Lymph node ratio (LNR) from ipsilateral and contralateral LNs was defined as the ratio of metastatic nodes to harvested nodes on each side.

Results

Patient Characteristics

About 67 patients underwent total thyroidectomy with bilateral lymph node dissections, including lateral neck nodes, during the study period, and 56 patients were ruled out under the exclusion criteria. Out of 11 enrolled patients, 3 patients were male and 8 patients were female, and the mean age at the time of surgery was 67.0 years (range 21-79 years). Six patients (54.5%) were under 45 years at the time of surgery, and 2 patients underwent multiple surgeries during the follow-up period (Table 1). About 8 patients received radioactive iodine treatment after surgery, and 3 patients were referred to other hospitals for further treatment.

Extent of Surgery and Distribution of Pathologic Lymph Nodes

The extent of neck dissection is summarized in Table 2. The pathologic report of 1 patient did not specify anatomic levels of pathologic LNs, so the reports of the remaining 10 patients were analyzed for the distribution of pathologic LNs. Among lateral LNs, pathologic LNs were mostly found in ipsilateral

Main Points

- Clinicopathologic characteristics of bilateral lateral lymph node (LN) metastasis in unilateral papillary thyroid cancer (PTC) were examined.
- All patients had central LN metastasis at the time of the surgery, and 72.8% of the patients had primary tumor larger than 2 cm.
- Aggressive subtype, gross extrathyroidal extension, and lymphovascular and perineural invasion, which are known to increase nodal metastasis in PTC, were not present in most of the patients.
- Preoperative ultrasonographic examination detected all possible contralateral lateral LN metastasis, while computed tomography missed some of the contralateral metastasis.

Table 1. Patient Demographics and Histopathologic Characteristics

Characteristics	n (%), n=11
Age, mean(range), years	67.0 (21-79)
<45 years	6 (54.5)
≥45 years	5 (45.5)
Sex	
Male	3 (27.3)
Female	8 (72.7)
Number of surgeries during follow-up period	
Single	9 (81.8)
Multiple	2 (18.2)
Tumor multiplicity	
Yes	3 (27.3)
No	8 (72.7)
Largest tumor size (mean ± SD)	2.75 ± 1.30 cm
≥2 cm	8 (72.7)
<2 cm	3 (27.3)
Aggressive variant	
Diffuse sclerosing variant	1 (9.1)
Gross extrathyroidal extension	
Present	2 (18.2)
Absent	9 (71.8)
Lymphatic invasion	
Present	3 (27.3)
Absent	8 (72.7)
Vascular invasion	
Present	0 (0.0)
Absent	11 (100.0)
Perineural invasion	
Present	1 (9.1)
Absent	10 (90.9)
Ipsilateral lymph node ratio* (mean ± SD)	0.42 ± 0.22
Contralateral lymph node ratio* (mean ± SD)	0.23 ± 0.13
Central node metastasis (level VI or VII)	
Present	11 (100.0)
Absent	0 (0.0)
Extranodal extension	
Present	6 (54.5)
Absent	5 (45.5)
Other pathology	
Nodular hyperplasia	1 (9.1)
Lymphocytic thyroiditis	1 (9.1)

SD, standard deviation.
*Lymph node ratio defined as the ratio of metastatic LN to harvested LN.

Table 2. Level of Lymph Node Dissection

Level	BOX_ITALIC
Ipsilateral	
Level II + III + IV + VI	2 (18.2)
Level II + III + IV + V + VI or VII	9 (81.8)
Contralateral	
Level II + III + IV + V	1 (9.1)
Level II + III + IV + VI	1 (9.1)
Level II + III + IV + V + VI	4 (36.4)
Level III + IV + VI	3 (27.3)
Level III + IV + V + VI	1 (9.1)
Level III + IV + VI + VII	1 (9.1)

Table 3. Level of Pathologic Lymph Nodes

Level	n(%), n = 10*
Ipsilateral	
Level II	6 (60.0)
Level III	9 (90.0)
Level IV	7 (70.0)
Level V	4 (40.0)
Level VI or VII	10 (100.0)
Contralateral	
Level II	2 (20.0)
Level III	6 (60.0)
Level IV	7 (70.0)
Level V	2 (20.0)
Level VI or VII	7 (70.0)

*Pathologic report of Patient number 6 was excluded from analysis

level III (9 patients, 90.0%) and bilateral level IV (7 patients each, 70.0%) (Table 3).

Histopathologic Characteristics

Of 11 patients, 3 patients (27.3%) had multiple tumors in the thyroid, and the mean size of the largest tumor was 2.75 cm (range 0.8-5.5 cm). About 8 patients had tumors larger than 2 cm (72.8%), and 1 patient showed an aggressive variant (11.1%, diffuse sclerosing variant). Gross extrathyroidal extension was present in 2 patients (18.2%), lymphatic invasion was present in 3 patients (27.3%), perineural invasion was present in 1 patient (9.1%), and vascular invasion was not present in any patients. The mean (SD) LNR of the ipsilateral and contralateral sides were 0.42 (0.22) and 0.23 (0.13), respectively, and extranodal extension was found in 6 patients (54.5%). Other than PTC, nodular hyperplasia and lymphocytic thyroiditis were noted in 1 patient each (14.3%) (Table 1).

Accuracy of Preoperative Evaluation on Lateral Lymph Node Metastasis

All 11 patients underwent preoperative US and computed tomography (CT) to evaluate the primary tumor and LN status. Radiologic report for preoperative CT was missing for 1 patient, and those for preoperative US were missing for the other 2 patients. For the remaining 8 cases, preoperative CT missed suspicious lateral LN metastasis for 1 patient, while preoperative US detected lateral LN metastasis in all patients.

Discussion

Each thyroid lobe has its own lymphatic drainage system without communication to the opposite side, and malignant cervical LNs of PTC are more likely to develop from level III and IV than II in the lateral compartment.[9,10] While level VI involvement increases the risk of lateral cervical metastasis, PTCs from the upper pole of the thyroid have a higher chance of skipping metastasis to level II and III.[10-14] Despite a controversy in whether nodal metastasis in PTC affects the long-term survival of low-risk patients, insufficient LN dissection increases cervical recurrence, leading to subsequent surgeries and lower quality of life.[6,15] Therefore, controlling locoregional recurrence through appropriate management of cervical LNs would be the major concern in the treatment of PTC.

Although there are limited studies regarding contralateral lateral LN metastasis in unilateral thyroid cancer, Kim et al[16] reported that unilateral PTC patients with male gender, primary tumor size > 2 cm, aggressive subtype, central node metastasis, and Delphian node metastasis are at a higher risk of contralateral lateral LN metastasis. Previous study of N1b PTC concluded that N1b PTC with tumors larger than 4 cm, tumor multiplicity, bilobar involvement, and bilateral central LN metastasis increased the risk of contralateral lateral LN metastasis.[17] In our study, 54.5% of the enrolled patients were under the age of 45 at the time of surgery, 72.8% of the patients showed tumors larger than 2 cm (18.2% larger than 4 cm), extranodal extension was present in 54.5% of the patients, and all patients had central compartment metastasis. Although we could not carry out further statistical analysis due to the limited number of cases, most of our patients shared some of the risk factors with the previous studies, especially the primary tumor size and central node metastasis. On the other hand, aggressive subtypes and gross extrathyroidal extension, which are known to increase nodal metastasis in PTC, were identified in only 1 patient (9.1%) and 2 patients (18.2%), respectively. Also, lymphovascular and perineural invasions, which reflect the aggressiveness of the disease, were not present in most of the patients (Table 1).[18,19]

In the present study, levels III and IV were most involved among ipsilateral lateral LNs, which coincides with the past study, and contralateral lateral LN metastasis was also focused on the same compartment even without contralateral lobe involvement (Table 3).[5] Meanwhile, the mean LNRs for the ipsilateral and contralateral compartments were 0.42 and 0.23, respectively. Lymph node ratio is used in conjunction with other staging systems in gastric and colon cancers, but there is a debate regarding the significance of LNR in PTC patients. Still, some studies reported LNR as an independent prognostic factor with a suggested clinical cut-off point of 0.3-0.42, and since the implication of LNR is still a field of ongoing research in PTC, it would be beneficial for surgeons to take it into account during the postoperative follow-up period.[20,21]

Past studies regarding cervical metastasis of PTCs were mostly focused on central LNs, partially because central node metastasis is relatively common in PTCs, reaching up to 50%.[22] However, the significance of lateral LN status on overall survival is more emphasized than that of central LN in several studies.[23,24] Since central LNs can easily be reached in the same operation field during thyroid surgery, many operators routinely perform central LN dissection even in low-stage PTC patients. In contrast to central LN dissection, lateral neck dissection commonly involves more scarring, operation time, recovery period, and possibly leaves more sequelae for the patients, so prophylactic lateral LN dissection is neither recommended nor routinely performed in clinical practice. Therefore, it is important to determine the extent of lateral LN surgery based on a thorough preoperative evaluation.

Ultrasonography is commonly used for preoperative evaluation of thyroid cancer and LN status to establish surgical plans, but the preoperative US may miss about half of the LNs identifiable through surgery.[10,25,26] However, in this study, preoperative US predicted lateral LN involvement in all patients, while preoperative CT missed lateral LN metastasis in 1 patient. Therefore, preoperative US is mandatory for patients with possibly advanced disease for more accurate surgical planning. Occult lateral LN involvement is known to be present in 20%-69% of clinically N0 PTCs, and factors such as age < 45 years, male sex, ETE, tumor location in upper pole, tumor size >10 mm, positive central LN metastasis, and vascular invasion are related to microscopic lateral LN metastasis.[27-29] Compared to unilateral LN metastasis, bilateral LN metastasis increases the risk of distant metastasis, affecting both locoregional recurrence and the overall survival rate in PTC.[30] Since lateral LN dissection is recommended in patients with biopsy-proven or suspicious metastatic lateral LNs, clinical suspicion of possible contralateral LN involvement even in unilateral PTC patients may contribute to increased detection of neglected nodal disease, leading to improved overall survival.[4]

Limitations

This study has some limitations. First, heterogeneity in the operative methods of surgeons may have affected the detection rate of metastatic LNs. Second, only a small number of cases were enrolled, maybe due to the rarity of the targeted disease. Third, this study was retrospective in nature. A future study with a larger sample size would be valuable for the accurate evaluation of risk factors associated with contralateral lateral LN metastasis in unilateral PTC patients.

Conclusion

Contralateral lateral LN metastasis is often overlooked in unilateral PTC patients, and large tumor, extrathyroidal extension, or central compartment metastasis could increase the risk of such disease. Since lateral LN involvement significantly affects the quality of life of the patient, meticulous evaluation using sonography for high-risk patients is necessary to detect possible occult contralateral lateral LN metastasis even in unilateral PTC.

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