Clinical and Ultrasonographic Features of Papillary Thyroid Carcinoma Located in the Isthmus

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Abstract: The aim of this research was to investigate the clinical and ultrasonographic features of papillary thyroid carcinoma (PTC) in the isthmus. A total of 823 patients with 823 PTCs including 133 in the isthmus and 690 in the lateral lobe were included in our study. All patients were confirmed by postoperative pathology. The clinical and ultrasonographic characteristics were retrospectively analyzed and compared. Univariate analysis and multivariate logistic regression analysis were performed. Multifactor analyses showed that PTC in the isthmus was significantly different from PTC originating from the lateral lobe in aspect ratio, microcalcification, extrathyroidal extension, lymph node metastases, and lymph node density (P < 0.05, for all). The results indicated that the sonographic appearances of PTC in the isthmus were relatively atypical; however, it had a higher incidence of extrathyroidal extension, central lymph node metastasis, and a tendency of higher lymph node density. Therefore, more careful ultrasound evaluation should be performed for these nodules.

Key Words: thyroid cancer, isthmus, lateral lobe, ultrasonography, lymph node

Abbreviations: PTC = papillary thyroid carcinoma, US = ultrasound, LNM = lymph node metastasis, LND = lymph node density, CLNM = central lymph node metastasis, ETE = extrathyroid extension, FNAB = fine-needle aspiration biopsy

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Papillary thyroid carcinoma (PTC) is the most common thyroid malignancy, accounting for 80% of thyroid cancers. With the wide use of high-frequency ultrasound (US) and fine-needle aspiration biopsy (FNAB), the detection rate of PTC increased rapidly in recent years. Papillary thyroid carcinoma may occur in any part of the thyroid gland, including the bilateral lobes and isthmus. Because of the small size of the isthmus, the incidence of PTC in the isthmus is about 2.2% to 12.3%, which is less than that in the bilateral lobes. However, it is known to be associated with more aggressive clinical and pathological features, such as multifocality, capsular invasion, and lymphovascular invasion. Recent studies also showed that patients with PTCs in the isthmus had poorer prognoses compared with patients with PTCs located in the lateral lobe.

At present, the ultrasonic diagnosis of PTC in the isthmus is based on the study of many diagnostic indicators of PTC in the lateral lobe, including an irregular shape, microcalcifications, aspect ratio of ≥1, and extrathyroidal extension (ETE). However, the sonographic features of PTC originating from the isthmus have not yet been well documented in the literatures. To the best of our knowledge, there was only 1 study that 48 PTCs originating from the thyroid isthmus were compared with 96 PTCs originating from the lobes. The purpose of this current study was to compare the clinical features and ultrasonographic manifestations of PTC in the isthmus with those in the lateral lobe, to improve our understanding of PTC arising from the isthmus and to provide useful information for subsequent clinical management.

MATERIALS AND METHODS

Patients

The retrospective study was approved by the institutional ethics committee, and the informed consent from the patients was waived. From January 2016 to March 2019, a total of 823 PTC patients who were confirmed by postoperative pathology were enrolled in this study. The following were inclusion criteria: (a) a single PTC confirmed by postoperative pathology, (b) patients with PTC in the isthmus who had undergone total thyroidectomy and at least bilateral central compartment node dissection, (c) patients with PTC in the lateral lobe who had undergone hemithyroidectomy and at least unilateral central compartment node dissection, and (d) patients with no history of neck irradiation. The exclusion criteria were as follows: (a) concomitant with other type of malignant thyroid tumor such as medullary carcinoma, (b) concomitant with other thyroid nodules with malignant ultrasonographic appearances, (c) associated with elevated calcitonin level, and (d) patients with no complete clinical data.
US Examination

Ultrasound examinations of the thyroid and neck were performed. A US instrumentation (Aplio-500, Toshiba, Japan) with a frequency of 4 to 10 MHz linear probe was applied. Ultrasound examination was performed by one of 3 board-certified radiologists who were aware of the clinical findings. Patients lied in the supine position with the neck extended. Images of each suspicious nodule were obtained in both transverse and longitudinal orientations. The position of the lymph nodes detected on US was determined according to the American Joint Committee on Cancer classification, which divided cervical lymph nodes into seven levels. If suspicious lymph nodes were detected, transverse and longitudinal images were obtained and the different levels were labeled. Ultrasound-guided FNAB was performed for the suspicious lymph nodes. All images were recorded and uploaded to a picture archiving and communication system for further analysis.

Image Analysis

The sonographic features of the nodule were carefully evaluated, including size, location, margin, echogenicity, homogeneity, aspect ratio, microcalcification, halo, and the relationship to the capsule. According to the maximum diameter, it was divided into \( \leq 10 \) mm and \( >10 \) mm. Location was determined as the isthmus and lateral lobe. The division method involved the drawing of 2 straight lines perpendicular to the skin and intersecting the outer edge of the trachea on the cross-sectional image, and the zone inside the straight line was regarded as the isthmus. The margin was classified into regular and irregular. Compared with the surrounding thyroid parenchyma, echogenicity was divided into hypoechoic and nonhypoechoic, and homogeneity was divided into uniform and uneven. Aspect ratio was divided into taller than wide (aspect ratio, \( \geq 1 \)) and wider than taller (aspect ratio, \(<1 \)). Microcalcification, which was defined as a strong echo with the diameter \( \leq 1 \) mm, was classified as absent or present. Halo was defined as absent or present. Extrathyroidal extension was divided into none or present. When the lesion had capsular abutment of more than 25% of its perimeter on US, the nodule was classified as ETE. The US images were analyzed by 2 doctors with more than 10 years of experience in thyroid imaging. In case of any disagreement, consensus agreement was achieved by discussion.

Surgical Treatment

All the operations were performed by the same surgical team. Lobectomy plus at least ipsilateral central lymph node dissection was performed for the patients with a solitary lesion in the lateral lobe. Total thyroidectomy plus at least bilateral central lymph node dissection was performed for the patients with a solitary lesion in the isthmus. Dissection of central compartment lymph nodes included the prelaryngeal, pretracheal, and paratracheal basins.

If suspicious lymph nodes in the contralateral central compartment were confirmed by FNAB, bilateral central lymph node dissection was performed for the patients with a lesion in the lateral lobe. If suspicious lymph nodes in the lateral compartment were confirmed by FNAB, ipsilateral lateral lymph node dissection was performed. Lymph node specimens were extirpated and compared with lymph nodes identified on US, and histopathological examination was performed. The presence of lymph node metastases (LNMs) was determined by postoperative pathology. Depending on the different levels, the nodal status was classified as central lymph node metastases (CLNM) and lateral lymph node metastases. Lymph node density (LND) was calculated by dividing the total number of metastatic lymph nodes by the total number of nodes examined in pathology.

Statistical Analysis

SPSS version 21.0 statistical software was used for data analysis. The \( \chi^2 \) test was used for counting data. The \( t \) test was used for measurement data. The \( \chi^2 \) test was used for single factor analysis, the indicators with statistical significance (\( P < 0.05 \)) for single factor were further used for multifactor analysis, and quadratic logistic regression was used. The difference was regarded as statistically significant, when \( P \) value was <0.05.

RESULTS

Clinical and Pathological Features of PTC in the Isthmus and Lateral Lobe

The clinical features of PTCs in the isthmus and lateral lobe were summarized in Table 1. The average ages of the 2 groups were 45.52 ± 13.10 years (range, 16–87 years) and 45.86 ± 11.73 years (range, 21–76 years), respectively. Of 823 thyroid nodules, 133 were located in the isthmus, and 58 cases had LNMs. There were 690 cases of PTCs in the lateral lobes, and 210 were associated with LNMs. The maximum diameter of the nodules ranged from 2.4 to 62.5 mm in the lateral group and 2.4 to 45.0 mm in the isthmus group, with an average size of 11.31 ± 8.69 mm and 10.61 ± 7.61 mm, respectively. There were significant differences in lymph node metastasis (LNM) and CLNM between these 2 groups (\( P < 0.05 \) for both). The incidences of LNM and CLNM in the isthmus group and lateral

| Characteristic | Lateral Lobe (n = 690) | Isthmus (n = 133) | \( P \) |
|---------------|------------------------|------------------|-------|
| Age, y        | 45.52 ± 13.10 (16–87)  | 45.86 ± 11.73 (21–76) | 0.645 |
| Sex, n (%)    |                         |                  |       |
| Male          | 172 (24.9)              | 31 (23.3)        | 0.743 |
| Female        | 518 (75.1)              | 102 (76.7)       |       |
| Tumor size, mm| 11.31 ± 8.69 (2.4–62.5) | 10.61 ± 7.61 (2.4–45.0) | 0.238 |
| Tumor size, n (%)|                               |              |       |
| >10 mm        | 279 (40.4)              | 51 (38.3)        | 0.700 |
| \( \leq 10 \) mm| 411 (59.6)              | 82 (61.7)        |       |
| LNM, n (%)    |                         |                  |       |
| None          | 480 (69.6)              | 75 (56.4)        | 0.005 |
| Present       | 210 (30.4)              | 58 (43.6)        |       |
| Nodal status, n (%)|                           |              |       |
| CLNM (+)      | 137 (19.9)              | 47 (35.3)        | 0.025 |
| LND (+)       | 73 (10.6)               | 11 (8.3)         | 0.801 |
| LND           | 0.38 ± 0.25 (0.05–1.0)  | 0.54 ± 0.30 (0.09–1) | 0.017 |

LLNM, lateral lymph node metastases.
The results of univariate analysis for sonographic characteristics were summarized in Table 2. There were no significant differences in margin, echogenicity, homogeneity, and halo between the isthmus and lateral lobe groups \((P > 0.05\) for all); however, significant differences were found in aspect ratio, microcalcification, and ETE between the 2 groups \((P < 0.05\) for all). The incidences of aspect ratio, microcalcification, and ETE in the isthmus group and lateral lobe group were 32.3% and 51.7% \((P < 0.001)\), 43.6% and 57.8% \((P = 0.003)\), and 56.4% and 11.4% \((P < 0.001)\), respectively.

### Multivariate Logistic Regression Analysis of Clinical and Sonographic Features

The results of multivariate logistic regression analysis for clinical and sonographic characteristics were summarized in Table 3. Between the 2 groups, there were no significant differences in patient’s age, sex, or nodule size, and there were no significant differences in margin, echogenicity, homogeneity, and halo. Compared with PTCs in the isthmus, microcalcification and an aspect ratio of \(\geq 1\) were more frequently detected in PTCs in the lateral lobe \((P < 0.001)\). There is a higher probability of ETE and a higher rate of LNM in the isthmus group \((P < 0.001)\). Significant difference was also detected in CLNM between these 2 groups \((P = 0.024)\). Lymph node density was significantly higher in the isthmus group than that in the lateral lobe group \((P < 0.001)\).

### DISCUSSION

Papillary thyroid carcinoma is the most common malignant tumor of the endocrine system, and the incidence rate has increased significantly in recent years.\(^{15}\) Papillary thyroid carcinoma usually has indolent behavior, with a good prognosis; however, some tumors may present with local recurrence and distant metastases. There are many factors associated with the prognosis of PTC, including older age, male sex, a large tumor size, multifocality, ETE, and the presence of LNM or distant metastases.\(^{16-20}\) The isthmus locates directly in front of the trachea. It is the central part of the thyroid gland, connecting the left and right lobes. Although the incidence rate of PTC arising from isthmus is low, it has been reported to exhibit aggressive tumor characteristics.\(^{3,6,21}\) This present study showed that the

### TABLE 2. Single Factor Analysis of Sonographic Characteristics of PTC in the Isthmus and Lateral Lobe

| Parameter         | Nodule Location | Isthmus (133) | Lateral Lobe (690) | \(P\) | \(\chi^2\) |
|-------------------|-----------------|---------------|-------------------|------|-----------|
| Margin            |                 |               |                   |      |           |
| Regular           | 268 (38.8%)     | 56 (42.1%)    | 0.498             | 0.598|           |
| Irregular         | 422 (61.2%)     | 77 (57.9%)    |                   |      |           |
| Echogenicity      |                 |               |                   |      |           |
| Nonhypoechoic     | 92 (13.3%)      | 13 (9.8%)     | 0.320             | 1.189|           |
| Hypoechoic        | 598 (86.7%)     | 120 (90.2%)   |                   |      |           |
| Homogeneity       |                 |               |                   |      |           |
| Uniform           | 213 (30.9%)     | 46 (34.6%)    | 0.415             | 0.714|           |
| Uneven            | 477 (69.1%)     | 87 (65.4%)    |                   |      |           |
| Aspect ratio      |                 |               |                   |      |           |
| <1                | 333 (48.3%)     | 90 (67.7%)    | <0.001            | 16.814|           |
| \(\geq 1\)        | 357 (51.7%)     | 43 (32.3%)    |                   |      |           |
| Microcalcification|                 |               |                   |      |           |
| Absent            | 291 (42.2%)     | 75 (56.4%)    | 0.003             | 9.127|           |
| Present           | 399 (57.8%)     | 58 (43.6%)    |                   |      |           |
| Halo              |                 |               |                   |      |           |
| Absent            | 648 (93.9%)     | 130 (97.7%)   | 0.094             | 3.167|           |
| Present           | 42 (6.1%)       | 3 (2.3%)      |                   |      |           |
| ETE               |                 |               |                   |      |           |
| None              | 611 (88.6%)     | 58 (43.6%)    | <0.001            | 148.065|           |
| Present           | 79 (11.4%)      | 75 (56.4%)    |                   |      |           |

CI, confidence interval.

### TABLE 3. Multifactor Analysis Results of Clinical Characteristics and Ultrasonic Manifestations of PTC in the Isthmus and Lateral Lobe

| Characteristic   | B    | SE   | \(\chi^2\) | df | \(P\) Exp (B) | \(\chi^2\) | Lower Limit | Upper Limit |
|------------------|------|------|------------|----|--------------|------------|-------------|-------------|
| Microcalcification| 0.926| 0.232| 15.936     | 1  | <0.001       | 2.523      | 1.602       | 3.975       |
| Aspect ratio     | 0.824| 0.247| 11.143     | 1  | 0.001        | 2.279      | 1.405       | 3.698       |
| ETE              | -2.435| 0.238| 104.809    | 1  | <0.001       | 0.088      | 0.055       | 0.140       |
| LNM              | -0.620| 0.239| 6.721      | 1  | 0.010        | 0.538      | 0.337       | 0.860       |
| CLNM             | -0.823| 0.365| 5.082      | 1  | 0.024        | 0.439      | 0.215       | 0.898       |
| LND              | -1.829| 0.461| 15.722     | 1  | <0.001       | 0.160      | 0.065       | 0.396       |

\(B\), coefficient; \(\text{SE}\), standard error; \(\chi^2\), chi-square; \(df\), degrees of freedom; \(P\), probability; \(\text{Exp (B)}\), exponential of the coefficient; \(95\%\), confidence interval.
the results of previous studies. However, there were only 43 cases (32.3%) with an aspect ratio of ≥1 in the isthmus group, which indicated that it might not apply to PTCs in the isthmus. This may be related to the unique location of the isthmus in the thyroid gland. The isthmus is usually thin, and the normal thickness is generally not more than 4 mm. When PTC grows to a certain extent, its longitudinal growth rate slows down because of a limitation that is imposed by the thyroid capsule and external muscles. Therefore, transverse growth of an isthmus nodule may be less inhibited because of the thin dimension of the isthmus.

Microcalcifications also play an important role in the differential diagnosis of benign and malignant thyroid nodules, and it could be more commonly seen in PTCs. Microcalcifications are usually manifested in round or concentric under the light microscope, which are mainly induced by psammoma bodies with a tiny diameter of 10 to 100 μm. In this study, the incidences of microcalcification were 43.6% in the isthmus group and 57.8% in the lateral lobe group, and the difference was statistically significant (P = 0.003). According to a previous study reported by Hahn et al, there was no significant difference in the incidence of calcification between nodules in the isthmus and in the lateral lobe, which was not consistent with our result. In their study, calcification was simply classified as present or absent, without further classification. However, the presence of microcalcification was assessed in our study, which may explain the discrepancy.

This study also found that the incidence of ETE in the isthmus group was significantly higher than that in the lateral lobe group, which was consistent with previously published reports. Extrathyroid extension is well known as a related factor of the presence of LNM for differentiated thyroid carcinoma. Cervical LNM is an important factor affecting the prognosis in PTC patients. In a large sample of a case-control study, Lundgren et al showed that well-differentiated PTC with LNM could increase the risk of disease-related death by as much as 3-fold. In our study, central lymph node involvement was more commonly observed in the isthmus group, whereas lateral node involvement was similar for the two groups. The management of PTC confined to the thyroid isthmus has remained controversial. Huang et al suggested that an isthmusectomy or extended isthmusectomy was feasible for patients with well-differentiated thyroid carcinoma arising from the isthmus. An isthmusectomy does not require exploration of the tracheo-esophageal groove and identification of parathyroid glands and the recurrent laryngeal nerve, which could reduce the risk of postoperative complications. However, Song et al recommended that complete bilateral central neck dissection should be considered for PTC in the isthmus because of the

FIGURE 1. A 48-year-old woman with PTC originating from the lateral lobe. Longitudinal US image showed a hypoechoic mass (arrow) with an aspect ratio of >1, irregular margin and microcalcifications.

incidence was 16.2% (133 of 823), which was similar with the result previously reported. The sonographic features of PTC mainly included solid composition, hypoechogenicity, aspect ratio of ≥1, irregular margin, and microcalcifications. However, these features were mainly based on the studies of nodules in the lateral lobe. To the best of our knowledge, this was the largest sample size study of sonographic characteristics of PTC arising from the isthmus compared with PTC located in the lateral lobe. Our results showed that there were no differences in margin, echogenicity, homogeneity, and halo between the isthmus and lateral lobe groups; however, there were significant differences in aspect ratio and microcalcification.

The aspect ratio of thyroid nodule is of great significance in distinguishing benign and malignant tumors. It is generally considered that an aspect ratio of ≥1 is an important feature of malignant nodule 1, and the aspect ratio reflects the variation index in thyroid nodule shape, which is closely related to the growth mode of the thyroid nodule. Compared with PTCs, benign tumors have greater compressibility because benign tumors generally tend to be softer. Papillary thyroid carcinoma is less susceptible to probe compression, which also might result that standing-like shape occurs more frequently in malignant than benign tumors. In this study, it was a common sign in the lateral lobe group, and the proportion was as high as 51.7%, which was consistent with

FIGURE 2. A, A 55-year-old woman with PTC originating from the isthmus (arrow). Transverse US image showed a solid mass with an aspect ratio of <1 and ETE. B, Longitudinal US image showed several suspicious lymph nodes (arrow) in the right central compartment. C, Several suspicious lymph nodes (arrow) were also detected in the left central compartment.
high rate of bilateral CLNM. Our results indicated that a total thyroidectomy and central neck dissection seemed to be more appropriate than a less-than-total thyroidectomy for PTC in the isthmus. However, a prophylactic lateral neck dissection may not be necessary for patients with clinically negative nodes. Lymph node density is defined as the ratio of the number of positive lymph nodes to the total number of lymph nodes excised. It has been shown to play a predictive role for oral cavity, pancreatic, gastric, and colon and be superior to conventional nodal staging, which could be potential useful in identifying patients with poorer outcome who might benefit from more aggressive adjuvant treatments.29–33 As for thyroid cancers, a previous study investigated the utility of LND using large single-institute cohort. It showed that LND greater than 0.19 was independently related to an adverse disease-specific survival and overall survival.34 To the best of our knowledge, the LND of PTC between in isthmus and in lateral lobe has not been compared in the literatures. In this study, LND in the isthmus group was significantly higher than that of the lateral group, which might indicate a relatively poor outcome and the importance of routine central compartment dissection.

There were some limitations in this study: first, not all patients underwent lymph node dissection in the central and lateral cervical regions during surgery, and it is possible that there might have been some bias in the LND value. Second, patients with multiple lesions were excluded in our study; however, multifocality might also be associated with the presence of LNMs. Third, it is theoretically possible that other malignancies or benign nodules also might have exhibited atypical features compared with PTCs, but only PTCs were included in our study. This might lessen the value of our results. Finally, this study was a retrospective study. The follow-up results were incomplete, and no analysis was performed.

In summary, our results showed that patients with PTC arising from the isthmus had a higher incidence of ETE, CLNM, and a tendency of higher LND; however, the sonographic appearances were relatively atypical compared with those of PTCs located in the lateral lobe. Therefore, more careful US evaluation should be performed for the nodule and cervical lymph nodes.

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