

Original Article

Ultrasound findings for papillary thyroid carcinoma in the isthmus: a case-control study

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Abstract: This study compared ultrasound imaging characteristics of papillary thyroid carcinoma (PTC) located in the isthmus and those of tumors originating in the lobes, and used these findings to establish a diagnostic imaging strategy for isthmus tumors. From a retrospective review of the database held at our center, we identified 150 patients with single classic PTC located in the isthmus and treated between January 2014 and December 2014. All patients had undergone preoperative ultrasound imaging, total thyroidectomy, or lobectomy, along with an ipsilateral central compartment node dissection, and had postoperative follow-up for at least 12 months. As a control group, 239 patients with single classic PTC located in the lobe who had undergone total thyroidectomy with bilateral central lymph node dissection during the same period were randomly selected and matched with the study group for age, sex, and tumor size. On clinicopathologic analysis, the incidence of extrathyroidal extension was higher in patients with a tumor originating in the isthmus than in the controls ($p < 0.001$). According to the imaging analysis, tumors originating in the isthmus more frequently had a circumscribed margin ($p < 0.001$) and a wider-than-tall shape ($p < 0.001$), and were more suspicious for extrathyroidal extension ($p < 0.001$) than those originating from the lobes. The results of this study show that PTCs originating in the isthmus are more likely to have extrathyroidal extension than those originating from the lobes. Therefore, careful ultrasound evaluation should be performed on masses in the thyroid isthmus even if ultrasound shows a circumscribed mass with a wider-than-tall shape.

Keywords: Thyroid, isthmus, papillary thyroid carcinoma, ultrasound

Introduction

Papillary thyroid carcinoma (PTC) is the most common follicular cell-derived thyroid malignancy and is considered a relatively indolent tumor from which death is rare. However, in the elderly and in patients exposed to radiation, PTC can behave aggressively [1, 2].

The thyroid isthmus lies directly anterior to the trachea, overlying the second to fourth tracheal rings, is covered by the strap muscles, fascia, and skin in the middle of the neck, and connects the right and left thyroid lobes. The frequency of isthmus nodules is unknown. A few studies have reported a lower prevalence (2.5%-9.2%) for nodules located within the thyroid isthmus than for nodules located in the lateral lobes of the thyroid [3-6]. Well-differentiated carcinoma arising within such nodules in the isthmus is reported to account for 1%-9% of all malignant thyroid nodules [3, 4, 7, 8]. However,

investigators have reported that PTCs arising in the isthmus are more likely to invade adjacent tissues, such as the trachea and strap muscles, than PTCs located in the other parts of the thyroid [3, 8, 9].

The surgical treatment for PTCs located in the isthmus remains controversial based on anatomic and biological characteristics. The American Thyroid Association, British Thyroid Association, and European Thyroid Association have developed recommendations for well-differentiated thyroid cancer, but there are no precise guidelines for the management of patients with dominant thyroid nodules of the isthmus [10, 11].

Among the modern imaging modalities for examining the thyroid gland, high-resolution ultrasound has been widely used in preoperative and follow-up examinations to detect primary and metastatic PTC tumors and to provide

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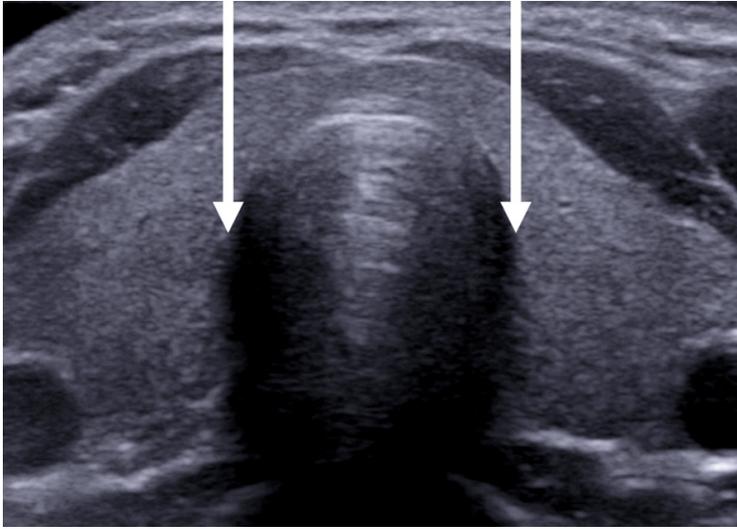


Figure 1. Ultrasound image of the thyroid in a 32-year-old healthy female control subject. To divide the thyroid gland into isthmus and lobe, we defined the lateral border of the isthmus by drawing two imaginary lines (arrows) perpendicular to the skin surface from the most lateral borders of the trachea.

critical information on the extent of surgery required [12-14]. Ultrasound findings indicative of a suspicious malignant mass include a taller-than-wide shape, a spiculated margin, marked hypoechogenicity, and microcalcifications [14-16]. These findings are primarily based on papillary carcinoma arising in the lobe, which accounts for most cases of thyroid carcinoma.

In the present study, we analyzed the ultrasound findings and clinicopathologic features in patients with papillary carcinoma originating in the isthmus and investigated how these tumors differ from PTCs that originate in the lobes.

Materials and methods

Patients and imaging methods

The images and medical records used in this retrospective study were provided by the Cancer Center of Fudan University. This study was approved by the Institutional Review Board of Fudan University Affiliated Cancer Center. We enrolled 150 patients with a single PTC located in the isthmus, who underwent thyroidectomy and neck dissection at our institution between January 2014 and December 2014 (group I). We also included a control group of 239 randomly selected patients who underwent thyroidectomy and neck dissection during the same period for a single PTC located in a

unilateral thyroid lobe and were matched with the study patients for age, sex, and tumor size (group II).

All patients underwent preoperative ultrasound imaging studies to evaluate the location of the primary tumor. Isthmic PTC was defined as a single tumor with its boundaries medial to the imaginary lines on the lateral margins of the trachea, based on preoperative ultrasound imaging studies and intraoperative findings. On the ultrasound imaging, we defined the lateral border of the isthmus by drawing two imaginary lines perpendicular to the surface of the skin from the most lateral points of the trachea (**Figure 1**) on the transverse scan. If the center of the thyroid mass was located between these two imaginary lines, we classified it as a mass originating in the isthmus even if its margin crossed these two imaginary lines.

Exclusion criteria were other pathologic type of thyroid cancer, multiple malignant nodules, a recurrence, and a subtype of PTC, such as follicular, oncocytic, tall cell, columnar cell, diffuse sclerosing, solid, or insular-variant PTC, because these subtypes have different imaging and clinicopathologic features.

All patients underwent total thyroidectomy or lobectomy along with an ipsilateral central compartment node dissection. If the tumor was located exactly in the midline in group I, prelararyngeal, pretracheal, and anterosuperior mediastinal node dissections were performed. Lateral neck dissection was performed only in patients with lateral compartment lymph node metastasis suspected on the basis of imaging studies or physical examination, or confirmed by fine-needle aspiration cytology. We did not perform prophylactic lateral neck dissection in patients with clinically negative lateral compartments.

Ultrasound was performed using a 5 MHz to 14 MHz linear array transducer (Logic E9, GE Healthcare, Milwaukee, WI, USA) or a 4 MHz to 15 MHz linear array transducer (Aixplorer, Super Sonic Imagine, Aix-en-Provence, France) by one of three board-certified radiologists who were

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Table 1. Comparison of clinicopathologic characteristics between PTC originating in the isthmus and the lobes

| | | Number or tumors (n) Percent (%) | | p-value |
|-----------------------------|-----------------------|----------------------------------|------------------|---------|
| | | Group I (n=150) | Group II (n=239) | |
| Reason for imaging | Screening | 133 (88.7) | 212 (88.7) | 0.932 |
| | Palpable mass | 5 (3.3) | 9 (3.7) | |
| | Other symptoms | 12 (8.0) | 18 (7.5) | |
| Distant metastasis | | 0 (0) | 0 (0) | 1.000 |
| Lateral neck dissection | Not done | 132 (88.0) | 197 (82.4) | 0.424 |
| | Unilateral | 15 (10.0) | 35 (14.6) | |
| | Bilateral | 3 (2.0) | 7 (2.9) | |
| Capsular invasion | | 106 (70.7) | 98 (41.0) | <0.001 |
| Recurrence during follow-up | | 1 (0.6) | 2 (0.8) | 0.669 |
| Nodal status | Central node positive | 65 (43.3) | 73 (30.5) | 0.007 |
| | Lateral node positive | 4 (2.6) | 32 (13.4) | <0.001 |

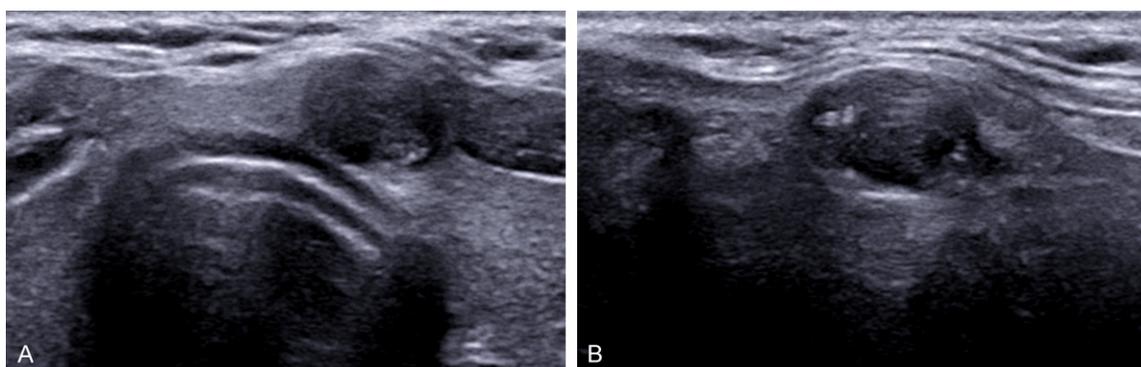


Figure 2. A papillary thyroid carcinoma (PTC) originating in the isthmus of a 24-year-old man. Transverse (A) and longitudinal (B) ultrasound images show a 10.5 mm × 7.2 mm hypoechoic mass with a circumscribed margin, wider-than-tall shape, broad abutment to the anterior capsule (> 25%), and anterior capsular bulging. After surgery, the diagnosis was PTC arising in the isthmus without lymph node metastasis. According to the pathology report, there was no extrathyroidal extension despite an ultrasound finding suspicious for the same.

aware of the clinical findings. Ultrasound examinations were performed for evaluation of the thyroid glands and neck.

Imaging data

The ultrasound findings for all the thyroid masses were retrospectively reviewed by two radiologists with 5 and 15 years of experience in thyroid imaging, respectively, and a final assessment of each case was made by consensus.

The following ultrasound findings were recorded: margin, shape, and internal echogenicity of the mass and presence of calcifications, cystic changes, and an ultrasound finding suspicious for extrathyroidal extension. The margin was classified as being either circumscribed or not circumscribed, and the shape was categorized

as being wider-than-tall or taller-than-wide. Taller-than-wide shape was defined as a mass that was greater in its anteroposterior dimension than its transverse dimension. Internal echogenicity was classified as hyperechogenicity, isoechogenicity, hypoechogenicity, marked hypoechogenicity, or anechogenicity. When the echogenicity of the mass was similar to that of the thyroid parenchyma, we classified it as isoechogenicity. Marked hypoechogenicity was defined as decreased echogenicity compared with the surrounding strap muscle. The presence or absence of calcifications and cystic changes was also evaluated. When the malignant mass had capsular abutment of more than 25% of its perimeter on ultrasound, the mass was classified as having ultrasound findings suspicious for extrathyroidal extension [17, 18].

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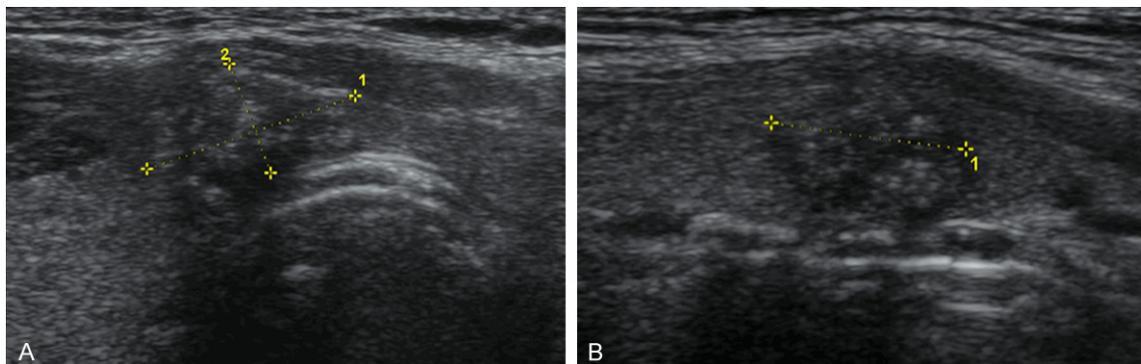


Figure 3. A papillary thyroid carcinoma (PTC) originating in the isthmus in a 43-year-old man. Transverse (A) and longitudinal (B) ultrasound images show a 13.5 mm × 7.1 mm hypoechoic mass with a noncircumscribed margin, a wider-than-tall shape, microcalcifications, broad abutment to the anterior capsule (> 25%), and anterior capsular bulging. After surgery, the diagnosis was PTC arising in the isthmus with central lymph node metastases and extra-thyroidal extension.

Table 2. Association between distribution of lateral neck lymph node metastases and mass location in PTC originating in the isthmus and in the lobes

| Mass location | Lateral lymph node metastases | | | |
|-------------------|-------------------------------|---------------------------|---------------------|-----------------|
| | Right unilateral (n=61) | Left unilateral (n=66) | Bilateral (n=11) | None (n=241) |
| Isthmus | | | | |
| Right side (n=64) | 1 | 0 | 0 | 63 |
| Left side (n=71) | 0 | 3 | 0 | 68 |
| Midline (n=15) | 0 | 0 | 0 | 15 |
| Lobe | | | | |
| Right (n=117) | 15 | 0 | 2 | 100 |
| Left (n=122) | 0 | 12 | 3 | 107 |

Statistical analysis

All patient data were analyzed including age at diagnosis, gender, tumor size, capsular invasion, coexisting thyroiditis, multifocality, central and lateral lymph node involvement, and post-operative complications. Student's *t*-test, chi-square test, and Fisher's Exact test were used, as appropriate, to compare differences between two groups. A *p*-value ≤ 0.05 was considered to indicate statistical significance. All statistical analyses were performed using SPSS version 20 software (IBM Corp., Armonk, NY).

Results

The mean tumor size in group I was larger than that in group II (8.36 ± 4.14 mm vs. 6.66 ± 2.65, respectively; *p*<0.001). There was no statistically significant difference in age (45.51 ± 11.93 vs. 44.65 ± 11.29; *p*=0.476) or female-to-male ratio (2.26 vs. 3.05; *p*=0.199) between

the two groups. The mean tumor size was 7.31 ± 3.41 (range 2-25) mm.

Clinicopathologic analysis

The clinicopathologic characteristics of the two groups are shown in **Table 1**. Tumors in group I showed a higher frequency of pathology-confirmed capsular invasion (**Figures 2, 3**) when compared with tumors in group II (70.7% vs. 41.0%, respectively; *p*<0.001). The rate of pathologically positive lymph node metastasis in the central compartment was higher in group I than in group II (43.3% vs. 30.5%; *p*=0.007). In addition, the frequency of metastasis in the lateral compartment was lower in group I than in group II (2.6% vs. 13.4%; *p*<0.001). The surgical procedures performed were similar, i.e., unilateral (10.0% vs. 14.6%) and bilateral (2.0% vs. 2.9%) dissection (*p*=0.424). There was no significant difference with regard to the presence of distant metastasis at the time of diagnosis (0% vs. 0%; *p*=1.000) or recurrence during the follow-up period (0.6% vs. 0.8%; *p*=0.833).

Overall, 46.0% of patients with PTCs originating in the isthmus (n=69) and 43.9% of patients with PTCs originating in the lobes (n=105) had lymph node metastasis. Lateral neck dissection was performed only in cases with clinically evident node metastases. **Table 2** shows the correlation between location of the thyroid mass and distribution of lateral lymph node

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Table 3. Comparison of imaging characteristics between PTC originating in the isthmus and in the lobes

| Characteristic | | Number of tumors(n) Percent(%) | | p-value |
|---|----------------------------|--------------------------------|------------------|---------|
| | | Group I (n=150) | Group II (n=239) | |
| Margin | Circumscribed | 68 (45.3) | 62 (25.9) | <0.001 |
| | Not circumscribed | 82 (54.7) | 177 (74.1) | |
| Shape | Wider-than-tall | 110 (73.3) | 112 (46.9) | <0.001 |
| | Taller-than-wide | 40 (26.7) | 127 (53.1) | |
| Internal echogenicity | Hyperechogenicity | 0 | 2 (0.8) | 0.058 |
| | Isoechogenicity | 12 (8.0) | 28 (11.7) | |
| | Hypoechoogenicity | 116 (77.3) | 154 (64.4) | |
| | Markedly hypoechoogenicity | 22 (14.7) | 52 (21.8) | |
| | Anechoogenicity | 0 (0) | 3 (1.3) | |
| Calcifications present | | 84 (56.0) | 130 (54.4) | 0.834 |
| Cystic changes present | | 3 (2.0) | 12 (5.0) | 0.178 |
| Ultrasound findings suspicious for extrathyroidal extension | | 121 (80.7) | 83 (34.7) | <0.001 |

metastases. Four unilateral cases (2.7%) and no bilateral cases (0%) were identified in group I, and 27 unilateral cases (13.4%) and 5 bilateral cases (2.1%) were identified in group II.

Imaging analysis

According to the analyses of ultrasound characteristics (**Table 3**), tumors originating in the isthmus had a higher incidence of the following findings than those originating in the lobes: a circumscribed margin (45.3% vs. 25.9%, respectively; $p < 0.001$; **Figure 2**), wider-than-tall shape (73.3% vs. 46.9%; $p < 0.001$; **Figures 2** and **3**), and ultrasound findings suspicious for extrathyroidal extension (80.7% vs. 34.7%; $p < 0.001$; **Figures 2, 3**). Among the thyroid masses with ultrasound findings suspicious for extrathyroidal extension (i.e., a tumor with capsular abutment $> 25\%$ of its perimeter), the 75.2% that originated in the isthmus (91/121 masses) and the 74.7% that originated in the lobes (62/83 masses) were pathologically confirmed to have extrathyroidal extension.

There were no significant differences between the groups with regard to: internal echogenicity, including hyperechoic (0% vs. 0.8%), isoechoic (8.0% vs. 11.7%), hypoechoic (77.3% vs. 64.4%), markedly hypoechoic (14.7% vs. 21.8%), and anechoic (0% vs. 1.3%; $p = 0.058$); calcifications (56.0% vs. 54.4%; $p = 0.834$); or cystic changes (2.0% vs. 5.0%; $p = 0.178$).

Discussion

A dominant thyroid nodule of the isthmus is an uncommon lesion and requires surgical evaluation. The limited data on the frequency of papil-

lary carcinoma arising in the thyroid isthmus indicate a range of 2.5%-9% [3, 5, 6]. Although the incidence of isthmic PTC is relatively low, these tumors are more likely to invade the adjacent tissues than PTCs located in other parts of the thyroid [3, 4, 9]. In this study, the rate of PTC arising in the isthmus was 5.4% (150/2754 patients), and similar to the values reported previously.

High-resolution ultrasound examination is becoming widely accepted as the technique of choice for staging PTC, and is recommended by the guidelines established by the American Thyroid Association to assess primary lesions and lymph node involvement. Ultrasound findings indicative of a malignant thyroid mass include a taller-than-wide shape, a spiculated margin, marked hypoechoogenicity, and microcalcifications or macrocalcifications [14-16]. We found that tumors originating in the isthmus more frequently had a circumscribed margin ($p < 0.001$) and a wider-than-tall shape ($p < 0.001$) on ultrasound examination when compared with the control group. These ultrasound characteristics appear to result from the tumors growing in the thin isthmus space. Therefore, a careful ultrasound evaluation should be performed for any mass that originates in the isthmus. Subtle hypoechoogenicity and presence of calcification could be clues as to whether ultrasound-guided fine-needle aspiration should be performed or not, even in cases where ultrasound has revealed a circumscribed mass with a wider-than-tall shape, which usually favors a benign diagnosis.

We also found that PTCs originating in the isthmus more frequently had pathologic extrathy-

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roidal extension than those originating in the lobes ($p < 0.001$). Among the various prognostic factors, extrathyroidal extension is a well-known prognostic factor for differentiated thyroid carcinoma, which is associated with a greater presence of lymph node metastasis, distant metastasis, local recurrence of disease, and tumor-related mortality [19-23].

The rate of central lymph node metastasis from isthmus PTC in our study was 43.3%, which was significantly higher than that of lobe-originating cancer (30.5%; $p = 0.007$) and similar to a previous finding by Lee et al (40.3%) [4]. In a retrospective review of patients who underwent central lymph node dissection for PTC, central lymph node metastasis was found in 41.2% of isthmus tumors [24].

However, among the 36 patients with lateral lymph node metastases, those with lobe-originating PTC tended to have unilateral lymph node metastases (84.4% [27/32]) while those with isthmus-originating PTCs had no bilateral lymph node metastases (0% [0/4]). We found that the rate of lateral neck dissection in patients with isthmus-originating PTCs was 12.0% (18/150). Again, this incidence is similar to that found by Lee et al (9.4% [17/181]) [4]. In other words, the incidence of preoperative diagnosis of lateral node involvement in our study was similar to that found by Lee et al. At our institution, lateral neck dissection is indicated only when metastatic PTC is diagnosed preoperatively. Bilateral node involvement was probably facilitated by spread through the intraglandular lymphatic networks that allow drainage between the lobes through the thyroid isthmus, followed by the extraglandular lymphatic networks that drain to the ipsilateral jugular chain of nodes. Awareness of this possibility would prompt more careful evaluation of the lymph nodes in the lateral neck compartments before surgery, thus leading to more accurate diagnosis.

We found no significant difference in clinical stage between the two groups. In this study, control subjects were selected randomly, were matched to the patients for age, sex, and tumor size, and had a single PTC in a unilateral thyroid lobe. This method of selection could have influenced the results of the statistical analysis with regard to clinical stage in the two groups. However, Lee et al [4] similarly reported that there was no significant difference in clinical stage between their two groups.

There are also several potential limitations to this study. First, it is a retrospective design and the fact that we only included patients with a single classic PTC who underwent total thyroidectomy or lobectomy along with an ipsilateral central compartment node dissection. Therefore, the study may have contained some degree of selection bias. Second, the data in the institutional database could have been incomplete. Third, we could not perform a statistical analysis for the pattern of distribution of lateral lymph node metastasis because of the limited sample size. Fourth, we did not statistically analyze the false-positive and false-negative results for ultrasound findings suspicious for extrathyroidal extension. In this study, 15 cases (6.3%) of lobe-originating PTCs were underdiagnosed and 15 (10%) of isthmus-originating PTCs were overdiagnosed as having extrathyroidal extension on ultrasound. These misdiagnoses were probably because of differences in parenchymal volume between the lobes and isthmus. Therefore, the ultrasound criterion for suspicion of extrathyroidal extension might need to be revised so that it differs by location.

In conclusion, the results of this study show that patients with isthmus-originating PTCs have a significantly higher incidence of extrathyroidal extension and higher rates of clinical, pathologic, and ultrasound imaging, and occult evidence of central lymph node metastasis than lobe-originating PTCs, although the tumor sizes and clinical stages are similar to those in patients with lobe-originating PTCs. Therefore, a careful ultrasound evaluation should be performed on a mass that originates in the isthmus. Ultrasound-guided fine-needle aspiration should be considered for isthmus PTC even in cases where ultrasound imaging shows a circumscribed mass with a wider-than-tall shape.

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Disclosure of conflict of interest

None.

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