Original Article

Implications of isthmic location as a risk factor in papillary thyroid carcinoma

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Background: Papillary thyroid carcinoma (PTC) located in the isthmus generally has been known to have more extrathyroidal extension (ETE), lymph node involvement, and multifocality. The purpose of this study was to determine the clinical significance of an isthmic location of PTC.

Methods: The records of 160 patients who underwent a total thyroidectomy due to a single, dominant isthmic PTC were retrospectively reviewed. The characteristics of isthmic cancer were compared with those of unilateral-lobar cancer in a PTC cohort at Seoul St. Mary's hospital. After propensity score matching for age, sex, and tumor size, 160 isthmic PTCs and 800 unilateral-lobar PTCs were compared. The clinicopathologic characteristics were analyzed to evaluate the prognostic significance of an isthmic tumor location.

Results: The isthmic group was significantly older (49.6 *vs.* 46.8 years, P=0.007) and had a smaller mean tumor size (0.8±0.4 *vs.* 1.0±0.7 cm, P<0.001) than the unilateral-lobar group. After propensity score matching, tumor size categories, ETE, multifocality, nodal metastasis and proportion of patients with more than five metastatic lymph nodes were similar in both groups. However, N1b cases were more frequent in the unilateral-lobar group both before and after propensity score matching. In multivariate analysis, isthmic location was not correlated with gross ETE, multifocality, and higher-risk N1 disease. Younger age and more than five metastatic nodes increased the risk of PTC recurrence. However, isthmic tumor location was not significantly correlated with recurrence-free survival.

Conclusions: Isthmic location is not an independent risk factor for aggressive clinicopathologic features and is not related to PTC recurrence.

Keywords: Papillary thyroid carcinoma (PTC); thyroid cancer; isthmus; lobe

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Introduction

Papillary thyroid carcinoma (PTC) located in the isthmus of the thyroid gland is relatively rare compared to PTC located in the two thyroid gland lobes (1-3). The isthmus is a thin thyroid parenchyma that connects both thyroid lobes anteriorly to the trachea. Isthmic PTC is more frequently associated with local invasion of adjacent tissues, bilateral lymph node involvement, and multifocality than PTC located in other parts of the thyroid gland (1-8). Therefore, many surgeons prefer total thyroidectomy and central compartment neck dissection (CCND) for primary treatment of PTC located in the isthmus (1,3,8-14).

Due to the indolent biologic behavior of PTCs and the steep increase of microcarcinoma, the treatment strategy of PTCs has become more conservative (15-18). Furthermore, the eighth edition of the tumor-node-metastasis (TNM) classification of the American Joint Committee on Cancer/Union Internationale Contre le Cancer (AJCC/UICC) staging system has decreased the negative prognostic value of lymph node metastases and microscopic extrathyroidal extension (ETE), and these changes have led to the significant downstaging of PTC patients (19,20). In the case of PTC located unilaterally in a thyroid lobe without gross ETE or clinical nodal metastasis, thyroid lobectomy has become the standard surgical procedure and is gradually replacing total thyroidectomy (21,22). However, due to their rarity and unique clinicopathologic characteristics, no clear consensus has been established for the management of isthmic PTCs (18).

Recently, some researchers have proposed isthmusectomy alone or a combination of isthmusectomy and lobectomy for isthmic PTC management, but the evidence regarding oncologic safety is still limited (2,3,23-25). The aim of this study was to investigate the clinical significance of an isthmic tumor location and its prognostic value in PTC patients by comparing the clinicopathological characteristics of isthmic and unilateral-lobar PTCs. We present this article in accordance with the STROBE reporting checklist (available at https://gs.amegroups.com/article/view/10.21037/gs-23-56/rc).

Highlight box

Key findings

- Clinicopathological characteristics of PTC located in thyroid isthmus are discussed.

What is known and what is new?

- PTC located in the isthmus generally known to have more aggressive pathological nature.
- Comparing PTCs located in unilateral lobe and isthmus, isthmic location is not an independent risk factor associated with aggressive clinicopathologic features and recurrence.

What is the implication, and what should change now?

- More conservative treatments like 'isthmusectomy' can be applied with oncological safety especially in early-stage lesions.

Methods

Patients

The medical records of PTC patients who underwent thyroidectomy at Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, from 2009 through 2013 were retrospectively reviewed. Patients with a single, dominant tumor, were categorized into two groups, isthmic or unilateral-lobe cancer, according to tumor location. Isthmic cancer was defined based on ultrasonography results when the center of the dominant tumor was located between two imaginary perpendicular lines extending from the most lateral point of the trachea. A dominant tumor located in a single thyroid lobe was categorized as unilateral-lobar cancer. Those with multiple cancers upon initial diagnosis were excluded. Of 175 single isthmic cancer patients who underwent total thyroidectomy, 160 were classical PTC subtypes and 15 were non-classical PTC subtypes including follicular, tall-cell, columnar-cell and diffuse sclerosing subtypes. Patients of all periods for follow up were included in this study.

The clinicopathological characteristics of isthmic cancer cases were compared with those of unilateral-lobar cancer cases in a PTC cohort at Seoul St. Mary's Hospital from 2009 to 2012. To analyze the complete pathological information of PTC such as invasion, lymph node involvement, and tumor multifocality, the medical records of PTC patients who underwent total thyroidectomy were retrospectively reviewed. The consecutive patients of 1,527 with unilateral-lobar PTCs who underwent total thyroidectomy according to guideline recommendations 25 and 26 issued by the American Thyroid Association (ATA) in 2009 were identified (26). Of these, 1,340 patients were classical PTC subtypes and 187 were non-classical PTC subtypes.

Prophylactic CCND was performed in clinically node-negative patients, and therapeutic node dissection was performed in cN1a and cN1b patients. Patients were

administered levothyroxine for thyroid stimulating hormone (TSH) suppression, and radioactive iodine therapy was performed within 6–8 weeks after surgery in patients who satisfied indications issued by the ATA guidelines (26). Serum thyroglobulin level measurements and neck ultrasonography were regularly performed every 6 or 12 months. None of the patients in this study had distant metastasis. Recurrence was defined as confirmed structural recurrence identified by image-guided cytology or histology.

All clinic histological data were reviewed. ETE was categorized as no, microscopic, or gross ETE according to the eighth edition of the AJCC/UICC staging system (20). Incidental multifocality was classified according to the size of the largest satellite nodule. Satellite nodule larger than 0.3 cm were considered clinically multifocal, and 0.3 cm or smaller were categorized as occult multifocal. In terms of nodal risk, patients with more than five metastatic lymph nodes (MLNs) were classified as having higher-risk N1 disease, and those with five or fewer MLNs were classified as having lower-risk N1 disease (18,27). The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the institutional review board of Seoul St. Mary's Hospital, The Catholic University of Korea (No. KC22RISI0058) and individual consent for this retrospective analysis was waived.

Statistical analysis

The clinicopathologic characteristics were analyzed to evaluate the prognostic significance of an isthmic tumor location. In order to reduce the bias of statistical analysis due to various subtypes with different prognoses, statistical analyzes were performed for classical subtypes which accounted for the majority. Propensity score matching (PSM) was used to adjust the baseline characteristics and reduce selection bias. Confounding variables, such as age, sex and tumor size, were included in the propensity score model. The isthmic group and the unilateral-lobar group were matched in 1:5 ratio. Continuous, quantitative data were expressed as mean ± standard deviation, and categorical, qualitative data were expressed as frequencies and percentages. The data were compared with the chi-square test, Mann-Whitney U test, or Student's *t*-test. Multivariate analysis was performed using logistic regression. Recurrence data were analyzed via the Kaplan-Meier method, log-rank test, and Cox proportional hazards model. The statistical analyzes for non-classical subtypes were also performed, respectively. All statistical analyses were performed using the SPSS version 28.0 (IBM, Armonk, NY, USA) and the R Integration Package 4.0.0 (R-Core Team, 2020).

Results

Patient characteristics before and after PSM in the classical PTC

The clinicopathologic features and outcomes of 1,500 patients with classical subtype of PTC are described in *Table 1*. We compared 160 patients with isthmic cancer and 1,340 patients with unilateral-lobe cancer. The follow-up period was 104.4±31.8 (range, 0–151) months. The mean patient age was 47.1±12.4 years; the mean tumor size was 1.0±0.6 cm. The isthmic group was significantly older than the unilateral-lobar group (49.6 *vs.* 46.8 years, P=0.007). The mean tumor size was smaller in the isthmic group than in the unilateral-lobar group (0.8±0.4 *vs.* 1.0±0.7 cm, P<0.001). However, when tumors were grouped by size, no difference was observed between the two groups. The ETE status, incidence of multifocality, and clinical multifocality were not significantly different between the two groups. In terms of nodal status, the incidence of nodal metastasis and higher-risk N1 disease were not different between the two groups. However, lateral neck node metastasis (N1b) was more frequent in the unilateral-lobar group than in the isthmic group (10.8% *vs.* 2.5%, P<0.001), although bilateral neck node metastasis was more frequent in the isthmic group than in the unilateral-lobar group (75% *vs.* 12.4%, P<0.001). The rate of recurrence and the recurrence-free survival time were not significantly different between the two groups.

After matching the isthmic group and the unilateral-lobar group using a 1:5 ratio according to age, sex and tumor size, 160 isthmic PTCs and 800 matched unilateral-lobar PTCs were compared (*Table 2*). The changes in the standard mean differences of factors in both groups before and after PSM are 0.148 to 0.037 for sex ratio, 0.231 to 0.052 for age, and 0.372 to 0.008 for tumor size. Age, sex and tumor size were comparable between the two groups after matching. There were no differences in terms of tumor size category, ETE, multifocality, or the rate of clinical multifocality between the two groups. Nodal metastasis and the proportion of patients with higher-risk N1 disease were similar in both groups. However, N1b cases were more frequent in the unilateral-lobar group than in the isthmic group (7.0% *vs.*

Table 1 Clinicopathologic characteristics of patients with classical subtype of PTC

Variables	Total patients (n=1,500)	Isthmic group (n=160)	Unilateral-lobar group (n=1,340)	P value
Age (years), mean ± SD [min–max]	47.1±12.4 [11–81]	49.6±12.1 [21–76]	46.8±12.4 [11–81]	0.007
Sex (male:female)	264:1,236	21:139	243:1,097	0.116
Tumor size (cm), mean ± SD [min–max]	1.0±0.6 [0.1–8.5]	0.8±0.4 [0.2–2.4]	1.0±0.7 [0.1–8.5]	<0.001
Tumor size (cm) in group, n (%)				0.052
≤1	1,012 (67.5)	123 (76.9)	889 (66.3)	
>1 to 2	402 (26.8)	32 (20.0)	370 (27.6)	
>2 to 4	82 (5.5)	5 (3.1)	77 (5.7)	
>4	4 (0.3)	0	4 (0.3)	
ETE, n (%)				0.964
None	724 (48.3)	76 (47.5)	648 (48.4)	
Microscopic	693 (46.2)	76 (47.5)	617 (46.0)	
Gross ETE	83 (5.5)	8 (5.0)	75 (5.6)	
Multifocality, n (%)				0.949
Absent	934 (62.3)	100 (62.5)	834 (62.2)	
Present	566 (37.7)	60 (37.5)	506 (37.8)	
Occult multifocality	277 (48.9)	34 (56.7)	243 (48.0)	0.205
Clinical multifocality	289 (51.1)	26 (43.3)	263 (52.0)	
Node metastasis, n (%)				0.477
No	696 (46.4)	70 (43.8)	626 (46.7)	
Yes	804 (53.6)	90 (56.3)	714 (53.3)	
1 ≤ MLN ≤ 5	583 (72.5)	72 (80.0)	511 (71.6)	0.091
MLN >5	221 (27.5)	18 (20.0)	203 (28.4)	
Lateral neck node metastasis, n (%)				
Absent	1,351 (90.1)	156 (97.5)	1,195 (89.2)	
Present (N1b)	149 (9.9)	4 (2.5)	145 (10.8)	<0.001
Ipsilateral	128 (85.9)	1 (25.0)	127 (87.6)	
Bilateral	21 (14.1)	3 (75.0)	18 (12.4)	<0.001
Recurrence	55 (3.7)	2 (1.3)	53 (4.0)	0.085
RFS (months) [95% CI]	146.3 [145.0–147.5]	149.2 [146.7–151.7]	145.9 [144.6–147.3]	0.093

PTC, papillary thyroid carcinoma; SD, standard deviation; ETE, extrathyroidal extension; MLN, the numbers of metastatic lymph node; RFS, recurrence-free survival; CI, confidence interval.

2.5%, P=0.032), whereas bilateral N1b cases were more common in the isthmic groups than in the unilateral-lobar group, even after PSM (75% *vs.* 5.4%, P<0.001). The recurrence rate and recurrence-free survival time did not differ between the two groups (*Table 2* and *Figure 1*).

Risk factors associated with aggressive features

Multivariate logistic regression was performed to identify independent risk factors associated with aggressive clinical features in matched isthmic and unilateral-lobar cancer

Table 2 Comparison between clinicopathological characteristics of the isthmic group and the unilateral-lobar group in classical PTC after 1:5 propensity score matching in age, sex and tumor size

Variables	Isthmic group (n=160)	Unilateral-lobar group (n=800)	P value
Age (years), mean ± SD [min–max]	49.6±12.1 [21–76]	49.0±12.1 [18–78]	0.549
Sex (male:female)	21:139	95:705	0.658
Tumor size (cm), mean ± SD [min–max]	0.8±0.4 [0.2–2.4]	0.8±0.4 [0.1–2.8]	0.931
Tumor size (cm) in group, n (%)			0.515
≤1	123 (76.9)	607 (75.9)	
>1 to 2	32 (20.0)	178 (22.3)	
>2 to 4	5 (3.1)	15 (1.9)	
ETE, n (%)			0.583
None	76 (47.5)	396 (49.5)	
Microscopic	76 (47.5)	377 (47.1)	
Gross ETE	8 (5.0)	27 (3.4)	
Multifocality, n (%)			0.696
Absent	100 (62.5)	513 (64.1)	
Present	60 (37.5)	287 (35.9)	
Occult multifocality	34 (56.7)	139 (48.4)	0.246
Clinical multifocality	26 (43.3)	148 (51.6)	
Node metastasis, n (%)			0.126
No	70 (43.8)	403 (50.4)	
Yes	90 (56.3)	397 (49.6)	
1 ≤ MLN ≤ 5	72 (80.0)	315 (79.3)	0.890
MLN >5	18 (20.0)	82 (20.7)	
Lateral neck node metastasis, n (%)			
Absent	156 (97.5)	744 (93.0)	
Present (N1b)	4 (2.5)	56 (7.0)	0.032
Ipsilateral	1 (25.0)	53 (94.6)	
Bilateral	3 (75.0)	3 (5.4)	<0.001
Recurrence	2 (1.3)	25 (3.1)	0.19
RFS (months) [95% CI]	149.2 [146.7–151.7]	147.1 [145.5–148.6]	0.202

PTC, papillary thyroid carcinoma; SD, standard deviation; ETE, extrathyroidal extension; MLN, the numbers of metastatic lymph node; RFS, recurrence-free survival; CI, confidence interval.

patients (*Table 3*). Gross ETE showed a positive correlation with the patient age, larger tumor size category, and more than five MLNs. Higher-risk N1 disease, which was defined as more than five MLNs, increased in patients with male sex, younger age, larger tumor size, gross ETE, and multifocality. The presence of multifocality was only correlated with more than five MLNs. However, isthmic location was not correlated with gross ETE, higher-risk N1 disease, or multifocality. Cox regression analysis was performed to compare recurrence-free survival between the two groups (*Table 4*). Younger age and having more than five MLNs increased the risk of recurrence. However, an

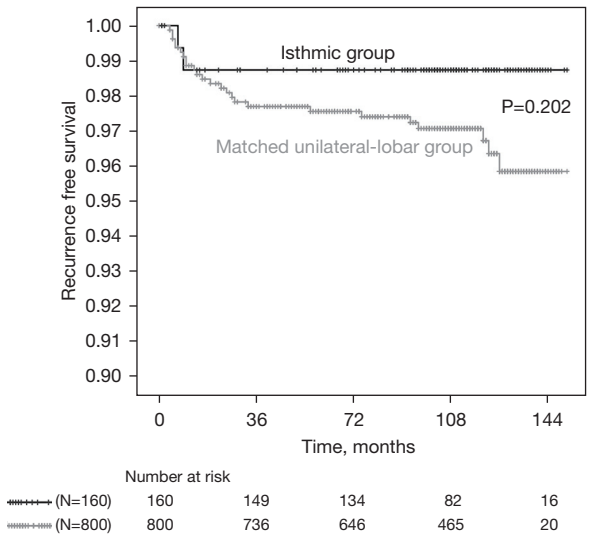

Figure 1 Recurrence-free survival curves of the isthmic group and the matched unilateral-lobar group in classical PTC. PTC, papillary thyroid carcinoma.

isthmic tumor location was not significantly correlated with recurrence-free survival time.

Patient characteristics in non-classical subtypes

We analyzed 15 patients with isthmic cancer and 187 patients with unilateral-lobe cancer which had non-classical subtypes of PTC (*Table 5*). The follow-up period was 95.4±26.2 (range, 14–140) months. There was no statistical difference in the proportion of non-classical subtypes in the two groups (15/175 in the isthmic group *vs.* 187/1,527 in the unilateral lobar group, P=0.155). The mean tumor size was smaller in the isthmic group than in the unilateral-lobar group (0.7±0.3 *vs.* 1.4±1.1 cm, P<0.001), and this difference continued to the tumor size in group (P=0.028). The mean patients' age, sex ratio, ETE, incidence of multifocality and nodal factors were not significantly different between the two groups. The eight recurrences occurred in only unilateral lobar group of non-classical subtypes of PTC and the rate of recurrence were not significantly different between the two groups.

Discussion

The increasing incidence of small thyroid cancer over time and the accumulation of cancer outcome data have led to more detailed interpretations of various prognostic factors (18,20,26). Microscopic ETE is no longer considered an independent prognostic factor for disease recurrence or survival. Therefore, microscopic ETE is considered as an intrathyroidal lesion in the eighth edition of the AJCC/TNM cancer staging system (18,28). The frequent, hidden, microscopic multifocal lesions of PTC have been used to justify performing 'total thyroidectomy' or 'completion thyroidectomy after thyroid lobectomy' (26,29,30). However, recently, the current approach is to perform total thyroidectomy only when clear evidence supports the removal of the contralateral thyroid gland, and the completion thyroidectomy is recommended only when total thyroidectomy would have been recommended if the diagnosis had been available before the initial surgery (18). Nodal risk is stratified according to the number of MLNs, the size of the metastatic foci, and the presence of extranodal extension (18,27). Accordingly, the treatment of PTC is gradually becoming more conservative than in the past (18,20,21,31).

The anatomic location of the isthmus contributes to frequent ETE, bilateral lymphatic spread, and multiple PTC lesions (1-8). Due to these clinicopathologic features, many surgeons insist on performing a total thyroidectomy with CCND to treat isthmic PTC (1,3,8-14). However, most evidence remains based on past prognostic factors or stages (1,4,6,9-12). For select patients, researchers suggested isthmusectomy as a feasible treatment option for isthmic PTC, although this remains controversial (2,3,23-25).

As isthmic cancer is rare, no studies have analyzed the above-mentioned, up-to-date prognostic factors for isthmic PTC. In this study, we analyzed the clinicopathological features of isthmic PTCs compared with those of unilateral-lobar PTCs. Furthermore, we investigated whether an isthmic location is related to PTC recurrence.

In isthmic cancer, the adjacent structures, including strap muscles and the trachea, are vulnerable to invasion because of the thin thyroid parenchyma. Chang *et al.* and Lee *et al.* reported that isthmic cancer showed more frequent thyroid capsule invasion than uni-lobular cancer (1,9,32). By contrast, Lyu *et al.*, Li *et al.*, and Song *et al.* reported no significant difference in the incidence of ETE (7,11,12). However, as any invasions beyond the thyroid capsule were defined as ETE in these studies, the actual incidence of gross ETE in isthmic PTCs cannot be accurately assessed. In this study, the isthmic and unilateral-lobar groups did not show significant differences in microscopic or gross ETE before or after PSM. Furthermore, an isthmic tumor location was not an independent risk factor for gross ETE

Table 3 Multivariate analysis for independent risk factors associated with extrathyroidal extension, multifocality and metastatic lymph node in classical PTC

Variables	Gross ETE		Multifocality		MLN >5	
	HR [95% CI]	P value	HR [95% CI]	P value	HR [95% CI]	P value
Isthmic location	1.607 [0.673–3.833]	0.285	1.086 [0.763–1.547]	0.647	1.141 [0.634–2.054]	0.66
Patients' age	1.033 [1.004–1.062]	0.026	1.002 [0.991–1.013]	0.746	0.949 [0.932–0.968]	<0.001
Male sex	0.369 [0.101–1.352]	0.132	0.787 [0.517–1.197]	0.263	2.532 [1.445–4.438]	0.001
Tumor size, cm						
≤1	Ref.		Ref.		Ref.	
>1 to 2	8.314 [3.535–19.555]	<0.001	1.295 [0.93–1.803]	0.126	4.085 [2.542–6.566]	<0.001
>2 to 4	20.322 [5.21–79.278]	<0.001	0.793 [0.296–2.128]	0.645	3.137 [1.001–9.834]	0.05
Gross ETE	N/A	N/A	0.689 [0.324–1.464]	0.333	5.121 [2.262–11.59]	<0.001
Multifocality	0.697 [0.325–1.494]	0.353	N/A	N/A	1.695 [1.076–2.67]	0.023
MLN >5	5.135 [2.256–11.686]	<0.001	1.675 [1.069–2.624]	0.024	N/A	N/A

PTC, papillary thyroid carcinoma; ETE, extrathyroidal extension; MLN, the numbers of metastatic lymph node; HR, hazard ratio; CI, confidence interval; Ref., reference; N/A, not applicable.

Table 4 Clinicopathological factors associated with recurrence-free survival in Cox proportional hazard model in classical PTC

Variables	HR [95% CI]	P value
Isthmic location	0.412 [0.097–1.753]	0.23
Patients' age	0.938 [0.906–0.972]	<0.001
Male sex	0.938 [0.32–2.75]	0.908
Tumor size, cm		
≤1	Ref.	
>1 to 2	1.181 [0.5–2.792]	0.704
>2 to 4	1.681 [0.217–13.016]	0.619
Gross ETE	1.433 [0.308–6.67]	0.646
Multifocality	1.1 [0.499–2.423]	0.813
MLN >5	4.397 [1.85–10.452]	0.001

PTC, papillary thyroid carcinoma; HR, hazard ratio; CI, confidence interval; Ref., reference; ETE, extrathyroidal extension; MLN, the numbers of metastatic lymph node.

in the multivariate analysis, whereas older age, lager tumor size, and more than five MLNs were associated with gross ETE. Most isthmic cancers were intrathyroidal or exhibited capsular invasion. Only 5% (n=8) of the isthmic group showed clinically significant gross invasion to strap muscles, and no tracheal invasion was observed in this study. Chung *et al.* reported that the anterior replacement of the strap muscle by thyroid cancer or obtuse angles between the thyroid cancer and trachea in ultrasonography are highly predictive of gross extrathyroidal invasion (33). Therefore, gross ETE of isthmic PTCs can be detected effectively in the preoperative evaluation.

Tumor multifocality is one of the features that advocated total thyroidectomy in isthmic PTC (1,5,10). However, Lee *et al.* reported that multifocality and bilaterality did not differ between isthmic and non-isthmic PTCs (1). Similarly, in our study, multifocality did not differ between the isthmic and unilateral-lobar groups before or after PSM. In the multivariate analysis, an isthmic location was not an independent risk factor for multifocality. To further analyze the characteristics of multiple incidental lesions, we classified satellite nodules according to their size. Since high-resolution ultrasonography can detect thyroid malignancies as small as 2 mm, satellite cancers with a size larger than 0.3 cm were considered clinically significant, and 0.3 cm or smaller were considered occult (34). Only 26 (16.3%) patients with isthmic PTCs exhibited clinical multifocality, and these clinical satellite lesions may be detected by careful preoperative ultrasonography.

The central location of the isthmus and its lymphatic drainage contribute to the bilateral nodal spread of PTC (6). Many reports have described frequent cervical node involvement in isthmic cancer, especially in the central compartment (7-9,11,12,32). An isthmic tumor location

Table 5 Clinicopathologic characteristics of patients with non-classical subtypes of PTC

Variables	Total patients (n=202)	Isthmic group (n=15)	Unilateral-lobar group (n=187)	P value
The proportion of patients with non-classical subtypes	11.9% (202/1,702)	8.6% (15/175)	12.2% (187/1,527)	0.155
Subtypes*, n (%)				0.641
Follicular	124 (58.2)	11 (73.3)	113 (57.1)	
Tall cell	53 (24.9)	4 (26.7)	49 (24.7)	
Columnar cell	7 (3.3)	0 (0.0)	7 (3.5)	
Oncocytic	6 (2.8)	0 (0.0)	6 (3.0)	
Diffuse sclerosing	1 (0.5)	0 (0.0)	1 (0.5)	
Others	22 (10.3)	0 (0.0)	22 (11.1)	
Age (years), mean ± SD [min–max]	48.9±12.4 [19–81]	47.47±11.7 [28–73]	48.96±12.4 [19–81]	0.653
Sex (male:female)	37:165	3:12	34:153	0.861
Tumor size (cm), mean ± SD [min–max]	1.34±1.1 [0.1–6.5]	0.7±0.3 [0.4–1.4]	1.4±1.1 [0.1–6.5]	<0.001
Tumor size (cm) in group, n (%)				0.028
≤1	114 (56.4)	14 (93.3)	100 (53.5)	
>1 to 2	55 (27.2)	1 (6.7)	54 (28.9)	
>2 to 4	25 (12.4)	0	25 (13.4)	
>4	8 (4.0)	0	8 (4.3)	
ETE, n (%)				0.703
None	128 (63.4)	8 (53.3)	120 (64.2)	
Microscopic	63 (31.2)	6 (40.0)	57 (30.5)	
Gross ETE	11 (5.4)	1 (6.7)	10 (5.3)	
Multifocality, n (%)				0.739
Absent	116 (57.4)	8 (53.3)	108 (57.8)	
Present	86 (42.6)	7 (46.7)	79 (42.2)	
Node metastasis, n (%)				0.529
No	110 (54.5)	7 (46.7)	103 (55.1)	
Yes	92 (45.5)	8 (53.3)	84 (44.9)	
1 ≤ MLN ≤ 5	61 (66.3)	4 (50.0)	57 (67.9)	0.307
MLN >5	31 (33.7)	4 (50.0)	27 (32.1)	
Lateral neck node metastasis, n (%)				
Absent	183 (90.6)	15 (100.0)	168 (89.8)	
Present (N1b)	19 (9.4)	0	19 (10.2)	0.195
Ipsilateral	19 (100.0)	N/A	19 (100.0)	
Bilateral	0	N/A	0	N/A
Recurrence	8 (4.0)	0	8 (4.3)	0.414
RFS (months) [95% CI]	136.3 [134.0–139.2]	N/A	136.3 [133.6–139.1]	0.421

*, cases with different subtypes in a single patient were also counted separately. PTC, papillary thyroid carcinoma; SD, standard deviation; ETE, extrathyroidal extension; MLN, the numbers of metastatic lymph node; RFS, recurrence-free survival; CI, confidence interval; N/A, not applicable.

was described as a strong independent risk factor for N1 disease (11,12). In a recent meta-analysis study about PTC located in the isthmus, Lyu *et al.* reported a significantly high rate of central lymph node metastasis in isthmic PTC (7). However, these studies analyzed risk factors only according to the presence or absence of node metastasis and did not classify the nodal risk according to the revised initial risk stratification of the ATA (18,27). The present study showed that the incidence of nodal metastasis and higher-risk N1 disease (more than five MLNs) were similar in both the isthmic and unilateral-lobar groups before and after PSM. In the multivariate analysis, higher-risk N1 disease was correlated with male sex, younger age, larger tumor size, gross ETE, and multifocality, but not with isthmic location. Lateral neck node metastasis was more frequent in the unilateral-lobar groups both before and after PSM. However, the rate of bilateral N1b disease was significantly higher in the isthmic group than in the unilateral-lobar group, likely due to bilateral lymphatic spread. Therefore, careful preoperative examination of both lateral neck nodes is recommended for isthmic PTCs.

In our study, 55 patients had recurrent disease, and the two groups showed similar recurrence rates. Younger patient age and higher-risk N1 disease were related to recurrence. However, an isthmic tumor location was not related to recurrence after PSM. These findings indicate that an isthmic location alone is not a poor prognostic factor for PTCs. Our results support evidence that isthmusectomy may a feasible treatment options in patients with small isthmic PTC. Our study has several strengths. This study is the first to analyze the clinicopathologic characteristics of isthmic PTCs by applying the most recent prognostic factors. Our study included a relatively large number of isthmic cancer patients compared with previous studies. All patients underwent total thyroidectomy and nodal dissection, therefore, histologic data, including multifocality and nodal involvement, were available. Furthermore, we performed the PSM to reduce selection bias between the two groups. However, our study also has limitations. This study is a retrospective study performed at a single institution. The nodal risk was assessed only by the number of MLNs, and the size of the metastatic foci or the presence of extranodal extension was not evaluated. Also, due to the limitation of the number of patients, only the classical PTC subtype was fully analyzed. Since preoperative ultrasound or cytological characteristics cannot predict the histologic subtype of PTC before surgery, additional research according to the non-classical PTC subtype located in the isthmic location is needed. Additionally, most patients in this cohort had early-stage disease with a small tumor size. Therefore, large-scale studies with patients in various disease stages are required to analyze the clinical implication of an isthmic PTC location.

Conclusions

An isthmic location alone is not an independent risk factor for aggressive clinicopathologic features and is not related to PTC recurrence in early-stage lesions.

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Footnote

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://gs.amegroups.com/article/view/10.21037/gs-23-56/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The institutional review board of Seoul St. Mary's Hospital, The Catholic University of Korea approved the study (No. KC22RISI0058) and individual consent for this retrospective analysis was waived.

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