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Lymph node metastasis characteristics of papillary thyroid carcinoma located in the isthmus

A single-center analysis

Genpeng Li, MD, Jianyong Lei, MD, Qian Peng, BS, Ke Jiang, MD, Wenjie Chen, MD, Wanjun Zhao, MD, Zhihui Li, MD, Rixiang Gong, MD, Tao Wei, MD, Jingqiang Zhu, MD, PhD*

Abstract

The frequency and pattern of lymph node metastasis and the extent of dissection for isthmic papillary thyroid carcinoma (PTC) remain unclear, and the aim of this present study was to evaluate these characteristics and to attempt to detect the best surgical protocol for isthmic PTCs. A total of 3185 consecutive patients with PTCs were reviewed. Of these patients, 47 with a single isthmic PTC were enrolled in our study, and matched 47 patients with a single PTC located in the unilateral lobe were randomly selected and added for comparison of their baseline tumor characteristics and lymph node metastasis characteristics. Univariate and multivariate analyses were performed to determine the risk factors for central lymph node metastasis in PTCs. The isthmic PTCs showed a higher rate of capsule invasion ($P = .013$) and advanced pathological N stage ($P = .038$) compared to the PTCs located in the lobe; meanwhile, pathological evidence of central lymph node metastasis ($P = .040$) was more frequent in the isthmic PTC group than in the control group. The univariate and multivariate analyses indicated that the tumors located in the isthmus (hazard ratio [HR]: 2.769; 95% confidence interval [CI]: 1.124–6.826; $P = .027$) and those with advanced (T2–4) pathological classifications (HR: 4.282; 95% CI: 1.224–14.976; $P = .023$) were independent risk factors for central lymph node metastasis in PTC patients. Due to the higher rate of pathological central lymph node metastasis and independent risk factors for central lymph node metastasis, total thyroidectomy, and bilateral central lymph node dissection should be considered the standard surgical protocol for isthmic PTCs.

Abbreviations: BMI = body mass index, c = clinical, CND = central lymph node dissection, NLR = neutrophil-to-lymphocyte ratio, p = pathological, PTC = papillary thyroid carcinoma.

Keywords: isthmus, lymph node, metastasis, papillary thyroid carcinoma

1. Introduction

The incidence of thyroid cancer is increasing rapidly, mainly as a result of recent advances in ultrasonographic screening and fine-needle aspiration biopsy.[1] Papillary thyroid carcinoma (PTC) is the most common histological type of differentiated carcinoma.[2] Although PTC has a very high 10-year survival rate of 93%, some special types exhibit an aggressive medical behavior.[3] Tumor location has been shown to be associated with neck metastasis.[4] There has been some interest in specific cases with rare locations and high biological activity, such as PTCs located in the isthmus, those with multiple foci and those with local invasion to adjacent tissues.[5] The thyroid isthmus lies directly anterior to the trachea, overlying the second to fourth tracheal rings and covered by the strap muscles, fascia and skin in the middle of the neck.[6] Only approximately 3% to 9.2% of all PTCs are located in the thyroid isthmus.[7] Because of the specific location and characteristics of these tumors, the surgical protocols for these patients remain controversial. Most studies have indicated that total thyroidectomy is an appropriate initial surgical procedure for isthmic PTCs.[6,7] Only 1 study has suggested that isthmusectomy alone might be a sufficient treatment for selected patients with small PTCs limited to the isthmus.[8] However, central compartment lymph node metastasis in isthmic PTCs remains unclear, and neither the American Thyroid Association nor the European Thyroid Association have issued precise guidelines for the

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Present address: Thyroid and Parathyroid Surgery Center, West China Hospital of Sichuan University, Chengdu 610041, China.

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Thyroid and Parathyroid Surgery Center, West China Hospital of Sichuan University, Chengdu, China.

** Correspondence: Jingqiang Zhu, MD, PhD, Thyroid and Parathyroid Surgery Center, West China Hospital of Sichuan University, Chengdu 610041, China (e-mail: zjqdoctor@163.com)*

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Table 1

Comparison of the baseline demographics and tumor features of patients with PTCs located in the isthmus and lobe.

	Isthmic PTC group	Control group (lobe)	
	47	47	*P*
Age at diagnosis (mean ± SD, y)	41.3 ± 11.5	38.6 ± 10.5	.240
≤55	43	45	.677
>55	4	2	
Sex (male/female)	10/37	11/36	.805
Height, cm	161.9 ± 6.5	162.7 ± 6.8	.593
Weight, kg	61.2 ± 12.0	62.1 ± 13.7	.751
BMI, kg/m^2	23.3 ± 3.9	23.4 ± 4.8	.865
Autoimmune thyroid disease (yes/no)	12/35	11/36	.811
Capsule invasion (yes/no)	27/20	15/32	.013*
Extrathyroid extension (yes/no)	10/37	6/41	.275
Tumor location (isthmus/left/right lobe)	47/0/0	0/27/20	<.001
Tumor size (mean ± SD, mm)	13.1 ± 6.5	14.4 ± 5.1	.274
≤5 mm	5	3	.088
5–10 mm	15	9	
≥10 mm	27	35	
Lateral lymph node dissection	4	2	.677
Number of dissected lymph node	9.5 ± 4.84	9.4 ± 5.17	.639
Number of metastatic lymph node	3.57 ± 3.74	2.81 ± 2.46	.512
p T classification (T1/T2/T3/T4)	36/1/9/1	39/2/6/0	.313
P N stage (N0/N1a/N1b)	17/26/4	27/18/2	.038*
p TNM stage (I/II/III/IV, AJCC version 8)	43/1/0/3	46/0/0/1	.361
NLR (mean ± SD)	1.9 ± 0.6	1.9 ± 0.7	.947
≤2	27	29	.676
>2	20	18	
PLR (mean ± SD)	110.8 ± 41.6	104.4 ± 49.9	.498
≤100	21	25	.412
>100	26	22	
TSH level (mU/L, mean ± SD)	4.6 ± 10.4	5.1 ± 10.7	.832

BMI = body mass index, NLR = neutrophil-to-lymphocyte ratio, p = pathological, PLR = platelet-to-lymphocyte ratio, SD = standard deviation, TSH = thyroid stimulating hormone.

* $P < .05$ indicates statistical difference.

surgical treatment of isthmic PTCs, particularly for prophylactic central compartment lymph node dissection.[9,10] Approximately 30% to 90% of patients with PTCs will have clinical or occult cervical lymph node involvement.[11] Therefore, in the present study, we attempted to evaluate the central lymph node metastasis characteristics and to determine the best surgical protocol for these patients with isthmic PTCs.

2. Patients and methods

The study design and protocol were approved by the Ethics Committee of the West China Hospital of Sichuan University. From Jan. 2009 to Aug. 2015, the medical records of 3185 consecutive patients with PTC were reviewed, including the patients' baseline characteristics, intraoperative data, postoperative recovery, and pathologic examinations. The inclusion criteria were patients from 18 to 80 years of age, with a single histopathological diagnosis of PTC who accepted total thyroidectomy and bilateral central neck dissection and had adequate medical histories available. The exclusion criteria were other pathological types of thyroid cancer, more than 1 tumor nodule, less-than-total thyroidectomy cases, and unilateral central neck dissection. Based on the inclusion and exclusion criteria, 42 isthmic cases with multiple tumors, including in the lobe, were excluded and 47 patients were enrolled with a single PTC target located in the isthmus who accepted total thyroidectomy and bilateral central neck dissection with or without lateral neck dissection. The control group for comparison consisted of randomly selected 47 patients with a single PTC located in the lobe who also accepted total thyroidectomy plus bilateral central neck dissection with or without lateral neck dissection and matched to group of isthmus PTC in well-established parameters, such as sex, age, body mass index (BMI), and size of the tumor. Of the control group, 27 left lobe PTCs and 20 right lobe PTCs were included in our study.

We retrospectively collected the clinical and tumor characteristics of these 2 groups of patients and the follow-up data in the outpatient system. Then, we compared the 2 groups of patients' baseline demographics, preoperative clinical and radiological evaluations, intraoperative data, postoperative recovery, pathological examinations, patterns of lymph node metastasis, and follow-up data. The central lymph nodes were divided into pretracheal and prelaryngeal lymph nodes, unilateral/bilateral paratracheal lymph node. Univariate and multivariate analyses were conducted to detect the risk factors for central lymph node metastasis. Locoregional recurrence was diagnosed by ultrasound or computer tomography (CT), combined with cytologic examination when necessary.

Ultrasound for the tumor and neck lymph nodes was used first to identify and diagnose the nodes in the thyroid; then, enhanced CT was also performed for all of the cases to identify other lymph node metastases in the neck. Ultrasonography-guided fine-needle aspiration cytology (FNAC) was performed on the tumor nodes in the thyroid and on nodes suspicious for central or lateral lymph node metastasis. The BRAF mutation could also help to diagnosis PTCs and to select surgical protocols. If FNAC could not diagnose, close observation and re-FNAC or intraoperative frozen section examinations were recommended to the patients. Prophylactic lateral neck dissection was not the routine surgical protocol for patients without confirmation on histological examination. Prophylactic central lymph node dissection (CND) was performed for all of the enrolled patients. CND was performed cranially to both superior thyroid arteries and to the pyramidal lobe, caudally to the innominate vein, laterally to the carotid sheaths, and dorsally to the prevertebral fascia.[12] All of the surgical procedures were performed by 1 of 3 experienced surgeons with at least 20 years of thyroid surgery experience. In the present study, the isthmus was defined as the thyroid tissue lying on the trachea but not beyond the lateral margins of the trachea, mainly based on the intraoperative findings.

All of the data were managed and the analysis was performed using SPSS software, version 17.0 (SPSS, Chicago, IL). Continuous variables were compared using nonparametric tests, and categorical variables were compared using the Chi-square test or Fisher exact test if necessary. The univariate analyses of correlations between central lymph node metastasis and clinicopathologic variables were performed using Pearson test, and variables with $P < .05$ on the univariate analyses were included in the multivariate analysis with dummy-variable binary logistic regression. The hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated to show significant differences. A difference was considered significant when $P < .05$.

3. Results

The baseline demographics and tumor characteristics were listed and compared between the 2 groups in Table 1. No significant differences were found between the 2 groups in age, sex, BMI, the

Table 2

Cervical lymph node metastasis characteristics and postoperative complications in the isthmic PTCs and unilateral lobe PTCs.

	Isthmic PTC group	Control group (lobe)	
	N = 47, %	N = 47, %	*P*
Cervical lymph node metastasis characteristics			
Pathological evidence of lymph node metastasis (p N+)	30 (63.8%)	20 (42.6%)	.040*
Central lymph node	19 (40.4%)	11 (23.4%)	.077
Pretracheal and Prelaryngeal lymph node	12 (25.5%)	16 (34.0%)	.370
Unilateral paratracheal lymph node	10 (21.3%)	4 (8.5%)	.044*
Bilateral paratracheal lymph node	4 (8.5%)	2 (4.3%)	.401
Lateral lymph node	23 (48.9%)	14 (29.8%)	.059
Occlut metastasis in c N−	26 (55.3%)	24 (51.1%)	.679
Postoperative complications			
Transient hypoparathyroidism	23 (48.9%)	23 (48.9%)	
Recurrent nerve palsy	0	0	.965
Transient hoarseness	2 (4.2%)	1 (2.1%)	
Postoperative bleeding	1	0	
Chylous fistula	0	0	
Infection	0	0	
Postoperative complications (Clavien–Dino system)	8 (17.0%)	7 (14.9%)	
I	4	5	
II	3	2	
III a	0	0	
III b	1	0	

c N− = clinical negative lymph node metastasis, P N+ = pathological positive lymph node metastasis.
* $P < .05$ indicates statistical difference.

presence of autoimmune thyroid disease, number of dissected lymph node and metastatic lymph node, and others (all $P > .05$).

When we compared the tumor features, we found that the isthmic PTC group had more cases with capsule invasion than the control group (57.4% vs 31.9%, $P = .013$). However, there were no differences between the 2 groups according to tumor characteristics, such as extrathyroidal extension and tumor size. According to the pathological evaluation, the isthmic PTC group showed significantly N ($P = .038$) classification than the control group. However, no significant differences were found in pathological T classification and TNM stages according to the AJCC system, version 8. The differences in the inflammatory factors, which can be related to cancer—the neutrophil-to-lymphocyte ratio (NLR) and the platelet-to-lymphocyte ratio also did not show statistically significant differences ($P > .05$).

Pathologically positive lymph node metastasis was significantly much more common in the isthmic PTC group than in the control group (especially in central compartment 63.8% vs 42.6%, $P = .040$); no significant differences were observed in the lateral lymph node metastasis rates. Although occult metastasis with negative preoperative clinical lymph node metastasis was more common in the isthmic group, this difference did not reach a statistically significant difference ($P = .059$). In the subgroup analysis of pathological evidence of central lymph node metastasis, no significant differences were observed in the pretracheal and prelaryngeallymph node metastasis rates between the 2 groups ($P > .05$). Bilateral paratracheal lymph node metastasis, however, was significantly more frequent in the isthmic PTC group (21.3% vs 8.5%, $P = .044$), as shown in Table 2. The postoperative complications were evaluated and compared between the 2 groups using the Clavien–Dindo system. The follow-up time of study population was 6 to 39 months, and mean time was 19.7 months. No patients suffered from permanent hypoparathyroid or recurrent laryngeal nerve injury (transient hoarseness due to tissue edema); only 1 patient in the isthmic PTC group suffered from postoperative bleeding and required reoperation. During the follow-up, 4 patients with sufficient lymph node yield from the initial operation suffered from recurrence at lateral region: 3 cases in the isthmic PTC group and 1 case in the control group.

As shown in Table 3, 14 variable clinical and pathological factors that could be associated with central lymph node metastasis were included in the univariate analysis. Five factors comorbid autoimmune thyroid disease, PTC located in the isthmus, pathological T classifications 2 to 4, NLR > 2 and thyroid stimulating hormone levels >2.5 mU/L were found to be associated with central lymph node metastasis in the univariate analysis. A multivariate analysis was performed for these significant factors that were identified in the univariate analysis,

Table 3

Univariate analyses of the clinical and pathological factors associated with central lymph node metastasis in PTCs.

		Central lymph node metastasis
Variables	N	*P*
Age at diagnosis (≤55/>55)	88/6	.6812
Sex (male/female)	21/73	.286
BMI (≤24/>24 kg/m^2)	66/28	.346
Autoimmune thyroid disease (yes/no)	23/71	.005*
Capsule invasion (yes/no)	42/52	.495
Extrathyroid extension (yes/no)	16/78	.175
Tumor location (isthmus/lobe)	47/47	.039*
Tumor size (≤5/>5 mm)	8/86	.852
Tumor size (≤10/>10 mm)	32/62	.383
c T classification (T1/T2–4)	89/5	.650
p T classification (T1/T2–4)	75/19	.021*
NLR (≤2/>2)	56/38	.044*
PLR (≤100/>100)	46/48	.155
TSH level (≤2.5/>2.5 mU/L)	50/44	.020*

BMI = body mass index, c = clinical, NLR = neutrophil-to-lymphocyte ratio, p = pathological, PLR = platelet-to-lymphocyte ratio, TSH = thyroid stimulating hormone.
* $P < .05$ indicates statistical difference.

Table 4

Multivariate analyses of factors contributing to central lymph node metastasis in PTCs.

Variables	Hazard ratio	95% CI	P
With autoimmune thyroid disease	1.088	0.378–3.131	.876
PTC located in isthmus	2.769	1.124–6.826	.027*
p T2–4 classification	4.282	1.224–14.976	.023*
NLR > 2	2.242	0.891–5.653	.086
TSH level > 2.5 mU/L	2.028	0.810–5.079	.131

CI = confidence interval, p = pathological, NLR = neutrophil-to-lymphocyte ratio, TSH = thyroid stimulating hormone.

* $P < .05$ indicates statistical difference.

which showed that PTCs located in the isthmus (HR: 2.769; 95% CI: 1.124–6.826; $P = .027$) and the pathological T2 to T4 classifications (HR: 4.282; 95% CI: 1.224–14.976; $P = .023$) represented significant risk factors for PTC central lymph node metastasis (as shown in Table 4).

4. Discussion

The isthmus is the central part of the thyroid gland that connects the thyroid lobes, and it is composed of thin (2–6 mm), small-volume thyroid parenchyma.[8] The proportion of PTCs that originate in the isthmus is very small, ranging from 1% to 9.2%,[7] and the present study found that the frequency of isthmic PTCs was 1.5% (47 of 3185). This difference might be explained by selection bias because we included only patients with 1 tumor located in the isthmus. Nevertheless, isthmic PTCs have been reported to exhibit aggressive tumor characteristics, including tumor multifocality, capsular invasion, extrathyroidal extension,[7] and, most importantly, lymph node metastasis.[5,11]

Because of the unique location and lymphatic drainage of the isthmus, surgical protocols for isthmic PTCs can differ from those for PTCs located in the lobe. Previous studies have evaluated and compared the appropriate extent of thyroidectomy for PTCs located in the isthmus: Nixon et al[8] suggested that isthmusectomy alone might be sufficient treatment for patients with small PTCs located in the isthmus, while avoiding dissection of the recurrent laryngeal nerve and parathyroid glands, thus limiting postoperative complications. However, most of these studies[6,7] recommended total thyroidectomy as the standard surgical protocol for isthmic PTCs because of higher tumor recurrence rate, and these results were consistent with our present study. Even among the previous studies, only a few have focused on the management of the lymph nodes and limited patient numbers.[5] According to a previous study based on anatomy,[13] the lymphatic system of the thyroid gland is parallel to the venous drainage system. In addition, lymphatic drainage of the isthmus might also contribute the higher lymph node metastasis rate because lymph vessels from the isthmus can drain into the pretracheal, prelaryngeal, and bilateral central compartment lymph nodes.[14]

As shown in our results, the capsule invasion rate was 57.4% in the isthmic PTC group, which was significantly higher than the 31.9% rate reported in the control group. The main reason for this difference might be the special anatomical structure: with tissue that is 2 to 6 mm thick and is covered by strap muscles,[8] even with smaller tumors, the isthmic PTC is more likely to invade the capsule, and capsule invasion cases are more likely to invade the surrounding tissue, which translates into a more advanced T stage. In addition, in the univariate and multivariate analyses, we demonstrated that an advanced T stage, PTCs located in the isthmus might contribute to central lymph node metastasis, and our result was consistent with other previous reports.[15,16]

Traditionally, the thyroid gland is divided longitudinally into an upper pole, middle third, lower pole, and isthmus.[11] Controversies remain regarding the correlation between tumor location and neck metastasis in patients with PTC.[11,17,18,19] In Lee et al[7] study, with 181 isthmic PTCs, the central lymph node metastasis rate was 40.3%, which was significantly lower than the rate of 63.8% in the present study. The main reason for this difference was that his study included multifocal tumors located in the lobe in some cases. However, Song et al[5] indicated that the prevalence of central neck compartment involvement reached 71.1% in the isthmic PTC group, which was almost in accordance with our study.

The rate of occult metastasis was 48.9% in the isthmic PTC group and less in the control group (29.8%), but this difference did not reach a statistically significant difference ($P = .059$). However, a larger cohort of cases might have yielded more objective results. The high rate of occult metastasis in the isthmic PTC group was mainly a result of the lower accuracy of the diagnosis of the central lymph node metastasis using preoperative ultrasonography, which is primarily the result of air disturbance from the trachea.[20] Therapeutic central neck dissection is a well-established surgical protocol for PTCs; however, the diagnosis of central neck lymph node metastasis is more difficult than metastasis in the lateral neck on ultrasonography, whereas FNA is impossible for the diagnosis of central neck lymph node metastasis because of the central neck's important anatomic structures. Prophylactic central neck dissection and the extent of such dissection in surgery for PTCs remains controversial.[21] Intraoperative frozen sections can help to identify the therapeutic or prophylactic extent of PTCs located in the isthmus or lobe: isthmusectomy alone might be sufficient treatment, as some studies have suggested.[8] The isthmic PTC group showed much more central lymph node metastasis (mainly bilateral paratracheal lymph node) than the group with PTCs located in the lobe; the main reason for this difference might be the location, which lies directly anterior to the trachea, overlying the tracheal rings in the middle of the neck; thus, metastasis is more likely to be bilateral with isthmic PTCs.[22]

The benefits of prophylactic central neck dissection include the following: first, approximately 30% to 90% of patients with PTCs will have clinical or occult cervical lymph node involvement[11]; thus, prophylactic central neck dissection makes it possible for us to accurately assess the stage of tumors and indirect the radioactive iodine therapy; furthermore, the risk of recurrence significantly increased with cervical lymph node metastasis and the second operation will increase the risk of postoperative complications[23]; importantly, tumor-free or overall survival can be improved effectively due to the removal of metastatic lesions in the central neck compartment.[24] The risks of prophylactic central neck dissection include hypoparathyroidism and recurrent laryngeal nerve injury.[25] To reduce the risk, some studies have recommended that only patients with certain clinicopathologic characteristics, including younger patients, male patients, those with larger tumor sizes, and extrathyroidal extensions, could take prophylactic central neck dissection into consideration.[5,26] However, in our postoperative complication comparison, no significant differences were observed between the 2 groups, and only 1 severe complication was observed. Furthermore, no cases suffered permanent

hypoparathyroidism or recurrent laryngeal nerve injury. Therefore, bilateral CND was shown to be safe in the present study, consistent with previous reports.[27,28]

Our present study had several limitations. First, the sample size of the group with isthmic PTCs was relatively small, likely because of the rarity of the disease, and to enhance the comparison, we excluded multiple PTCs located in the isthmus and in the lobe. Second, the retrospectively collected data and the absence of long-term follow-up might also have limited the study. Thus, larger sample sizes, the collection of data from multiple centers, and randomized trials with long-term follow-up should be included in future studies.

In conclusion, our study demonstrated that isthmic PTCs had more common pathological central lymph node metastases (especially bilateral paratracheal lymph node) than PTCs located in the lobe and it is an independent risk factor for central lymph node metastasis as well. Total thyroidectomy and bilateral central neck dissection should be considered as the standard surgical protocol for isthmic PTCs.

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