Risk factor for contralateral occult carcinoma in patients with unilateral papillary thyroid carcinoma

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Purpose: The extent of surgery necessary in patients with unilateral papillary thyroid carcinoma (PTC) on preoperative radiologic imaging is still in doubt. In this study, we aimed to define risk factors that could be indicators for malignant nodules in the contralateral thyroid lobe.

Methods: We included 438 patients who underwent total thyroidectomy between January 2011 and December 2014 at our institution. In this study, patients were divided into two groups according to the presence of contralateral occult carcinoma identified by postoperative pathological examination. We analyzed the clinicopathologic factors including characteristics of coexistent nodules in the contralateral lobe based on preoperative radiological imaging.

Results: A total of 96 patients (21.9%) had PTC in the contralateral lobe. There were no significant differences between patients with or without contralateral occult carcinoma with respect to gender, age, primary tumor size, central lymph node metastasis, extrathyroidal extension and stage. The presence of Hashimoto's thyroiditis was an independent predictive factor for contralateral occult carcinoma ($P=0.01$).

Conclusion: A risk factor for contralateral occult carcinoma in unilateral PTC patients is Hashimoto's thyroiditis. Therefore, more caution is needed when determining optimal surgical methods for PTC patients with Hashimoto's thyroiditis.

Keywords: Papillary thyroid carcinoma, Contralateral, Risk factor

INTRODUCTION

Papillary thyroid carcinoma (PTC) is the most common histological type of thyroid cancer, accounting for more than 80% of all thyroid cancer patients [1]. The incidence of PTC is increasing worldwide with the development of imaging techniques and growing interest in health [2]. The primary treatment for thyroid cancer is surgery. PTC patients who underwent unilateral thyroidectomy are known to have lower morbidity than those treated with total or near total thyroidectomy. The 2015 American Thyroid Association management guidelines for adult patients with thyroid nod-

ules and differentiated thyroid cancer recommends thyroid lobectomy if the tumor size is 4 cm or less, PTC is unifocal and intrathyroidal and no cervical lymph node metastasis is clinically found [3,4]. Lobectomy for PTC patients should be performed only when no contralateral occult carcinoma is detected by preoperative tests. There are cases of PTC where there are two or more separate foci within the thyroid gland. The rate of such multifocal PTCs has been reported to be 18% to 87% depending on the accuracy of diagnostic techniques [5]. The rate of preoperatively undiagnosed tumor foci incidentally detected by postoperative pathological analysis has been reported to be 15.8%–21.3% [6,7]. Preoperatively undiagnosed carcinomas in the contralateral lobe may lead to additional surgery due to postoperative remnant disease and may also be associated with regional and distant metastasis [1].

Therefore, this study aimed to identify risk factors for contralateral occult carcinoma based on imaging findings and pathological findings in patients preoperatively diagnosed with unilateral PTC and treated with total thyroidectomy.

METHODS

We carried out a retrospective review of the medical records of 1,613 PTC patients who underwent total thyroidectomy in the Di-

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vision of Breast and Thyroid Surgery of the Department of Surgery at Jeonbuk National University Hospital from January 1, 2011 to December 31, 2014. Among the patients, patients diagnosed with Korean Thyroid Imaging Reporting and Data System (K-TIRADS) category 4 or higher [8], which are intermediate malignant suspicion categories, in the contralateral lobe of primary tumor by preoperative ultrasonography and neck computed tomography (CT) were excluded from the study. Patients diagnosed with PTCs in both lobes by fine needle aspiration (FNA) and those who underwent completion thyroidectomy were also excluded. Thus, a total of 438 patients were enrolled in this study. All the patients were diagnosed with PTC by preoperative FNA, and preoperative ultrasonography and neck CT were performed to determine the presence or absence of extrathyroidal invasion and central lymph node metastasis. Contralateral occult carcinoma was defined as a lesion which is diagnosed as benign or low suspicion (K-TIRADS categories 2, 3) or is not detected (K-TIRADS category 1) by preoperative radiologic tests but diagnosed as malignant postoperatively by final histological examination. And contralateral occult carcinoma also includes occult malignant foci (OMF). Patients were divided into two groups according to the presence or absence of contralateral occult carcinoma based on the results of postoperative histopathologic examination. Then, we examined clinicopathologic factors of each group, such as age, sex, tumor size, the presence of pathologic Hashimoto's thyroiditis (HT), extrathyroidal invasion, the presence of cervical lymph node metastasis, and stage of cancer according to the American Joint Committee on Cancer (AJCC) cancer staging manual, 8th edition [9]. In addition, we also analyzed the association of postoperatively detected contralateral occult carcinoma with the number and size of benign tumors in the ipsilateral and contralateral lobes of PTC by preoperative ultrasonography and neck CT and the number and size of malignant and benign tumors identified by postoperative pathological findings.

Statistical analysis was conducted using R version 3.2.2 (R Foundation for Statistical Computing, Vienna, Austria). Univariate and multivariate logistic regression analyses were performed to investigate the relationship between clinicopathologic characteristics and contralateral occult carcinoma. A P-value < 0.05 was considered statistically significant. This study was conducted after obtaining the approval of the IRB of Jeonbuk National University Hospital (IRB No. 2019-07-020).

RESULTS

A total of 438 patients were enrolled in this study and the subjects consisted of 367 females and 71 males. The mean age of the pa-

tients at the time of surgery was 49.0 years (range, 15–6 years).

The mean thyroid stimulating hormone (TSH) level was 1.9 mIU/L, the mean tumor size was 10.3 mm (range, 5–43 mm), and 278 patients (63.4%) had micro PTC smaller than 1 cm in size. Central lymph node metastasis was detected in 255 patients (58.2%), HT in 309 patients (70.5%) and extrathyroidal extension (ETE) in 250 patients (57%) (Table 1).

In 96 patients (21.9%), contralateral occult carcinoma was detected by pathological examination after total thyroidectomy. The mean number of contralateral occult carcinoma was 1.18 (range, 1–3) and the mean size was 3.53 mm (range, 1–17 mm).

Table 1. Demographic characteristics of 438 patients with papillary thyroid carcinoma

Characteristics	Value (n = 438)
Sex	
Female	367 (83.7)
Male	71 (16.3)
Age at diagnosis (yr)	
< 55	305 (69.6)
≥ 55	133 (29.4)
TSH (mIU/L)	1.9 ± 1.5
Tumor size (cm)	
< 1	278 (63.4)
1 to < 2	121 (27.6)
2 to < 3	37 (8.4)
≥ 3	2 (0.4)
Central lymphnode metastasis	
Absent	255 (58.2)
Present	183 (41.8)
Hashimoto's thyroiditis	
Absent	309 (70.5)
Present	129 (29.5)
Extrathyroidal extension	
Absent	250 (57.0)
Present	188 (43.0)
Stage ^{a)}	
1	394 (89.9)
2	35 (7.9)
3	9 (2.0)
Contralateral lobe tumor K-TIRADS	
Category 1	119 (27.2)
Category 2	74 (16.9)
Category 3	245 (55.9)

Values are presented as number (%) or mean ± standard deviation.

TSH, thyroid stimulating hormone; K-TIRADS, Korean Thyroid Imaging Reporting and Data System.

^{a)}American Joint Committee on Cancer (AJCC) cancer staging manual, 8th edition.

Patients were divided into groups with and without contralateral occult carcinoma to investigate the relationship between clinicopathological characteristics and the presence of contralateral occult carcinoma. Table 2 shows analysis results of the association between clinicopathological characteristics and contralateral occult carcinoma. The clinicopathological characteristic significantly associated with contralateral occult carcinoma was the presence of HT ($P=0.01$). However, there were no statistically significant differences between the two groups in gender, age, TSH level, tumor

Table 2. Clinicopathologic characteristics in relation to contralateral occult carcinoma in 438 patients with papillary thyroid carcinoma

Characteristics	Contralateral occult carcinoma (–) (n = 342)	Contralateral occult carcinoma (+) (n = 96)	P-value
Sex			0.98
Female	286 (83.6)	81 (84.4)	
Male	56 (16.4)	15 (15.6)	
Age at diagnosis (yr)			1.00
< 55	238 (69.6)	67 (69.8)	
≥ 55	104 (30.4)	29 (30.2)	
TSH (mIU/L)	1.9 ± 1.4	1.9 ± 1.8	0.95
Tumor size (cm)			0.06
< 1	226 (66.1)	52 (54.2)	
1 to < 2	85 (24.9)	36 (37.5)	
2 to < 3	30 (8.8)	7 (7.3)	
≥ 3	1 (0.3)	1 (1.0)	
Central lymph node metastasis			1.00
Absent	199 (58.2)	56 (58.3)	
Present	143 (41.8)	40 (41.7)	
Hashimoto's thyroiditis			0.01
Absent	252 (73.7)	57 (59.4)	
Present	90 (26.3)	39 (40.6)	
Extrathyroidal extension			0.76
Absent	197 (57.6)	53 (55.2)	
Present	145 (42.4)	43 (44.8)	
Stage ^{a)}			0.77
1	306 (89.5)	88 (91.7)	
2	29 (8.5)	6 (6.2)	
3	7 (2.0)	2 (2.1)	
Contralateral lobe tumor K-TIRADS			0.06
Category 1	98 (28.7)	21 (21.9)	
Category 2	63 (18.4)	11 (11.5)	
Category 3	181 (52.9)	64 (66.7)	

Values are presented as number (%) or mean ± standard deviation.

TSH, thyroid stimulating hormone; K-TIRADS, Korean Thyroid Imaging Reporting and Data System.

^{a)}American Joint Committee on Cancer (AJCC) cancer staging manual, 8th edition.

size, central lymph node metastasis, ETE, AJCC stage, and K-TIRADS category of contralateral lobe tumor.

The cases without ipsilateral multifocal tumors were 172 patients (50.3%) and 42 patients (43.8%) in the group without contralateral occult carcinoma and the group with contralateral occult carcinoma, respectively, showing that ipsilateral multifocality was not associated with contralateral occult carcinoma. The mean number of cancer lesions in the ipsilateral lobe detected by preoperative ultrasonography was 1.34 (range, 1–6). In both groups, the mean number of benign nodules in the ipsilateral lobe was 0.7 (range, 0–9). Preoperative examination revealed multifocality in the contralateral lobe in 244 patients (71.3%) of the group without contralateral occult carcinoma and in 75 patients (78.1%) of the group with contralateral occult carcinoma, showing that there was no significant difference between the two groups ($P=0.23$).

Among patients in whom contralateral occult carcinoma was detected, 21 patients (21.9%) were found to have OME. The number of contralateral tumors classified as K-TIRADS category 3 or lower was 1.5 and 1.6 in the group without contralateral PTC and the group with contralateral occult carcinoma, respectively, indicating that there were no statistically significant differences between the two groups. In addition, the mean tumor size of the contralateral nodules categorized as K-TIRADS category 3 or lower

Table 3. Preoperative multifocality and tumor characteristics in relation to contralateral occult carcinoma in 438 patients with PTC

Variable	Contralateral occult PTC (–) (n = 342)	Contralateral occult PTC (+) (n = 96)	P-value
Ipsilateral lobe multifocality			0.30
Absent	172 (50.3)	42 (43.8)	
Present	170 (49.7)	54 (56.2)	
Ipsilateral cancer count			0.15
1	267 (78.1)	64 (66.7)	
2	53 (15.5)	24 (25.0)	
3	17 (5.0)	6 (6.2)	
4	2 (0.6)	2 (2.1)	
5	2 (0.6)	0	
6	1 (0.3)	0	
Ipsilateral benign tumor count	0.7 ± 1.2	0.7 ± 1.2	0.74
Contralateral lobe multifocality			0.23
Absent	98 (28.7)	21 (21.9)	
Present	244 (71.3)	75 (78.1)	
Contralateral benign tumor count	1.5 ± 1.5	1.6 ± 1.4	0.66
Contralateral benign tumor size (mm)	4.5 ± 5.1	4.4 ± 4.0	0.89
Bilateral tumor count	3.5 ± 2.5	3.7 ± 2.2	0.58

Values are presented as number (%) or mean ± standard deviation.

PTC, papillary thyroid carcinoma.

Table 4. Multivariate analysis for risk factor of contralateral occult carcinoma

Risk factor	OR	95% CI	P-value
Ipsilateral lobe multifocality	1.30	0.82–2.05	0.25
Contralateral lobe multifocality	1.33	0.78–2.24	0.28
Hashimoto's thyroiditis	1.91	1.19–3.07	0.01
Extrathyroidal extension	1.10	0.69–1.73	0.67
Lymph node metastasis	0.99	0.62–1.57	0.97
Primary tumor size	1.84	1.12–3.01	0.12

OR, odds ratio; CI, confidence interval.

was 4.5 mm and 4.4 mm in the without contralateral occult carcinoma group and the with contralateral occult carcinoma group, respectively; as such, there were no statistically significant differences between the two groups. Furthermore, the total number of thyroid nodules detected preoperatively was 3.5 and 3.7, respectively, so there was no statistically significant difference between the two groups (Table 3).

Four out of 119 patients (3.4%) who were in K-TIRADS category 1 had benign nodule in the contralateral lobe, and OMF in the contralateral lobe was in 21 patients (17.6%). Of the 74 patients who were in K-TIRADS category 2, 37 patients (50%) had benign nodule in the contralateral lobe, one patient (1.4%) had cancer and concurrent benign nodule, and 10 patients (13.6%) had cancer. Of the 245 patients who were in K-TIRADS category 3, 133 patients (54.3%) had benign nodule in the contralateral lobe, nine patients (3.7%) had cancer and concurrent benign nodule, and 55 patients (22.4%) had cancer.

Multivariate logistic regression analysis showed that HT is a risk factor for contralateral occult carcinoma and that primary carcinoma size, central lymph node metastasis, ETE, and multifocality were not associated with an increase in contralateral occult carcinoma (Table 4).

DISCUSSION

The American Thyroid Association guidelines [4] recommends total thyroidectomy for thyroid cancer larger than 4 cm in size, but the use of total thyroidectomy still remains controversial for thyroid cancer with a size of 4 cm or less, and the optimal extent of surgical treatment for PTC is still under debate [4–6]. In this study, we investigated whether primary tumor characteristics such as the size of primary tumor, multifocality, central lymph node metastasis, HT, and ETE, which are factors affecting the extent of surgical resection, are associated with contralateral occult carcinoma. We also analyzed the association of the size and number of benign and low malignant nodules in the contralateral lobe with contralateral

occult carcinoma.

Pitt et al. reported that 30% of patients with primary tumor of 1 cm or larger and 26% of patients with primary tumor smaller than 1 cm were found to have PTC in the contralateral lobe. It has been reported that primary tumor size was not significantly related to the presence of contralateral occult carcinoma [1,10]. In agreement with those findings, in the present study, contralateral occult carcinoma was present in 27.5% of patients with primary tumor with a size of 1 cm or greater and in 23.0% of patients with primary tumor smaller than 1 cm, so primary cancer size was not a significant predictive factor for the presence of PTC in the contralateral lobe.

Consistent with the results of Jo et al. [11], who reported that the mean size of contralateral OMF was 2 mm (range, 1–3 mm), in this study, the mean size of contralateral OMF was 1.89 mm (range, 1–6.6 mm) and the mean size of contralateral occult carcinoma was 2.33 mm. In the 2000s, the development of ultrasound enabled us to detect thyroid nodules with a size of 2 mm or greater [12]. However, among contralateral occult carcinomas, lesions smaller than 2 mm are still difficult to detect by ultrasonography. Therefore, OMF is likely to be identified only in pathologic reports, though the development of ultrasound technology is expected to make it possible to detect OMF by ultrasonography.

In the literature, the rate of multifocality of PTC ranges from 15% to 43% [13,14]. Kim et al. [15] reported that cancer multifocality of the ipsilateral lobe was a predictive factor for additional cancer in the contralateral lobe. Another study suggested that the presence of a benign nodule in the contralateral lobe may be an independent predictive factor for contralateral occult carcinoma in patients diagnosed with unilateral papillary thyroid microcarcinoma by preoperative ultrasonography [16]. However, in this study, multifocality including cancers and benign nodules in the primary tumor lobe was not significantly associated with the presence of contralateral occult carcinoma.

In this study, we investigated whether there are significant differences between the groups with and without contralateral occult carcinoma in the multifocality and size of contralateral lobe nodules classified as the K-TIRADS category 1 for no nodule, category 2 for benign (malignancy risk < 3%) and category 3 for low suspicion (malignancy risk 3%–15%) according to the K-TIRADS categories presented by the Korean Society of Thyroid Radiology. These findings are in contrast to the results of many previous studies that reported that multifocality is a risk factor for contralateral PTC [11,15,17,18]. This discrepancy in study findings may be attributed to the fact that the number of patients enrolled in this study was not sufficient to determine the significance of multifocality.

However, there were limitations on one-to-one matching of le-

sions preoperatively categorized as benign or low malignancy with lesions diagnosed as cancers by pathological examination. There are two main reasons for this problem. First, it was difficult to regard the lesions identified by preoperative ultrasound as identical to the lesions detected by pathological examination because the sizes of lesions measured by ultrasound preoperatively may become different according to the ultrasound views. Second, there were cases where a new lesion was detected at a different location in patients with benign lesions. These reasons are thought to be explained by the fact that the K-TIRADS categories of contralateral lobe nodules evaluated preoperatively were not significantly associated with the presence of contralateral occult carcinoma in this study.

The incidence of ETE in well-differentiated thyroid cancer reported in previous studies varies widely from 5% to 34% and it is known to be an important adverse prognostic factor [19-21]. Pitt et al. [1] reported that ETE of primary carcinoma smaller than 1 cm was not a risk factor for contralateral occult carcinoma. In a study by Jo et al. [11] on the risk factors for OMF in the contralateral lobe, ETE was present in 45% of patients without OMF and in 44.3% of patients with OMF, and there was no significant difference between the two groups. Similarly, in this study, ETE was found in 42.4% of patients without contralateral occult carcinoma and in 44.8% of patients with contralateral occult carcinoma; There was also no significant difference between the two groups ($P = 0.76$).

The true incidence of contralateral PTC is difficult to estimate in cases where total thyroidectomy is not performed [22]. The incidence of contralateral PTC identified in the specimens of patients who underwent CT or total thyroidectomy reported in the literature ranges from 13% to 56%, and, in this study, contralateral PTC was detected in 21.9% of patients [1,3,23]. Multivariate analysis of primary tumor characteristics showed that only the presence of HT was a significant risk factor for contralateral occult carcinoma. The association between HT and differentiated thyroid carcinoma has been studied in many previous studies [24]. Segal et al. [25] reported that HT is not a premalignant condition and it delays the growth and development of thyroid carcinoma. In contrast, Di Pasquale et al. [26] reported the increased incidence of papillary carcinomas associated with HT. In this study, the incidence of contralateral occult carcinoma was significantly higher in patients with HT than in patients without HT ($P < 0.01$). This finding is similar to the results of Bradley et al. [24] who reported that HT is a risk factor for incidental PTC. Therefore, contralateral lobe evaluation should be conducted more carefully in patients with HT, and total thyroidectomy may be considered as a treatment method to reduce potential morbidity such as remnant cancer, recurrence, and additional operations. If this study were analyzed with HT di-

agnosed with preoperative imaging or laboratory tests, it would have been useful in clinical practice. However, the readings were inconsistent because preoperative imaging was performed by many sonographers. In addition, preoperative antibody screening tests were limited because HT confirmed by laboratory tests were not covered by medical insurance. Therefore, unfortunately, we analyzed the data with pathologic HT.

The 10-year survival rate of PTC patients is reported to be more than 90% and PTC generally shows an excellent prognosis [10]. In the present study, among 438 patients, 10 patients became lost to follow-up, six patients had lymph node metastasis, and one patient had lung metastasis for 5 years after surgery. Total thyroidectomy may result in postoperative morbidity, including hypoparathyroidism in 6% of patients, recurrent laryngeal nerve injury in 1% of patients, and transient hypocalcemia [27]. PTC is a slow growing tumor and generally shows better prognosis compared to other histological types of thyroid cancer. In addition, thyroid lobectomy preserves thyroid function and has the advantage of the patient not needing lifelong thyroid hormone replacement. Therefore, thyroid lobectomy should be considered as a treatment option in unilateral PTC patients without HT.

This study has further limitations in that this is a single institutional study conducted with patients who underwent diagnosis and surgery at our medical institution, a tertiary general hospital, from 2011 to 2014, and that it is also a retrospective study. In addition, this study has limitations regarding the accuracy of preoperative thyroid ultrasonography because it was performed by an experienced specialist and a resident in the department of radiology of our medical institution. Therefore, the quality of research should be enhanced by conducting a multi-institutional study with more patients and an increase in the accuracy of ultrasound examination.

In the present study, among patients preoperatively diagnosed with unilateral PTC, 96 patients (21.9%) were found to have contralateral occult carcinoma. Among clinicopathologic characteristics, only HT was found to be a risk factor for contralateral occult carcinoma. Therefore, surgical methods for PTC patients with HT should be determined with more caution.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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