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Original Article

Multifocality of the primary tumor is a predictive factor for contralateral occult carcinoma in patients with unilateral papillary thyroid carcinoma

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Abstract: Purpose: To analyze the risk factors for occult contralateral carcinoma in the patients with unilateral thyroid papillary carcinoma (PTC). Methods: A retrospective review of the clinical data of PTC patients with total thyroidectomy from September 2012 to September 2014 in Zhejiang Cancer Hospital, was conducted to estimate the incidence of contralateral occult carcinoma of thyroid and to analyze the related risk factors. Results: A total of 300 patients with unilateral PTC were admitted in the present study. The rate of occult carcinoma in the contralateral lobe of thyroid was 18.3% (55/300). Contralateral occult carcinoma was not significantly associated with age, gender, the primary tumor size by ultrasonography and pathology, presence of Hashimoto's thyroiditis, capsular invasion, extraglandular extension, central lymph node metastasis, lateral cervical lymph node metastasis, or "benign" nodules in the contralateral lobe. The univariate analysis revealed that contralateral occult carcinoma was significantly increased in patients with multifocality of primary tumor (P=0.000). In multivariate analysis, mulifocality of primary tumor was an independent predictive factor for occult carcinoma in the contralateral lobe of thyroid gland (P=0.000, *odds ratio*=4.486). Conclusion: We demonstrated that the presence of mulifocality of primary tumor was an independent predictive factor for contralateral occult carcinoma in patients with unilateral PTC. The prediction of contralateral occult carcinoma in unilateral PTC according to pathological features, could be useful for determining the optimal extent of surgery.

Keywords: Papillary thyroid cancer, contralateral, occult, risk factors, carcinoma

Introduction

Papillary thyroid carcinoma (PTC) was a common malignant tumor, and the incidence of PTC was increased rapidly in the last decade. However, the surgical extent of unilateral PTC remains controversy. Total thyroidectomy was mostly performed for PTC >1 cm, but the management of microcarcinoma (diameter less than 1 cm) has not reached consensus. The presence of contralateral nodules in unilateral PTC is common in clinical work, and the optimal surgical extent of unilateral PTC remains a topic of debate. The rate of occult carcinoma in contralateral lobe ranged from 13 to 56% [1-5], and the inadequate surgical extent will increase the risk of local recurrence. It is worth further study on the predictive factors for contralateral occult carcinoma in unilateral PTCs. This retrospective analysis of the clinical data of patients with unilateral PTC who received total thyroidectomy, was conducted to investigate the incidence, clinical characteristics and predictive factors of contralateral occult carcinoma.

Materials and methods

Inclusion and exclusion criteria

The clinical data of 714 PTC patients who received total thyroidectomy from September 2012 to September 2014 at the Department of Head and Neck Surgery in Zhejiang Cancer Hospital was reviewed. The information was recorded as follow: age, gender, preoperative ultrasound results, the distribution and size of nodules, preoperative laboratory examination, postoperative pathology and laboratory exami-

Table 1. Demographic characteristics of 300 patients with unilateral papillary thyroid carcinoma

Demographic Characteristics	Negative Contralateral Carcinoma	Positive Contralateral Carcinoma	Total
No. Of Patients	245 (81.7%)	55 (18.3%)	300
Age (y)	49.19±11.34	47.45±12.44	48.87±11.54
Gender (M/F)	46/199	16/39	62/238
Hashimoto's Thyroiditis (Y/N)	43/202	7/48	50/250
Contralateral Lobe Nodules (Y/N)	217/28	49/6	266/34
Multifocality (Y/N)	46/199	28/27	74/226
Primary Tumor Size (cm)	0.98±0.67	1.14±1.17	1.01±0.85
Capsular Invasion (Y/N)	133/112	27/28	160/140
Extrathyroidal Extension (Y/N)	23/222	2/53	25/275
Central LNM (Y/N)	84/161	24/31	108/192
Lateral LNM (Y/N)	44/201	11/44	55/245

Abbreviations: y, year; M, male; F, female; Y, yes; N, no; LNM, lymph node metastasis.

nation. Sonographic characteristics for malignancy were defined as microcalcification, not circumscribed margins, marked hypoechogenicity, and taller than wide shape.

Inclusion criteria: (1) preoperative ultrasonography (US) or fine needle aspiration (FNA) showed definite PTC confined to only the unilateral lobe of thyroid, without suspicious carcinoma lesion in the contralateral lobe; (2) initial treatment in our hospital; (3) bilateral thyroidectomy; (4) postoperative pathology with PTC.

Exclusion criteria: (1) benign lesions and other types of thyroid malignancy; (2) initial treatment in other hospitals; (3) patients who received radiofrequency ablation; (4) preoperative US or FNA prompted bilateral suspicious or malignant nodules; (5) intraoperative frozen section or postoperative pathology suggested the intrathyroidal dissemination of tumor.

Pathological diagnosis

The samples were tested by intraoperative frozen section and postoperative routine pathology. The specimens after surgery were routinely sectioned every 3 mm. The pathologic features of primary tumor were recorded as follow: tumor size, multifocality, presence of Hashimoto's thyroiditis, presence of capsular invasion, extraglandular extension, and central or lateral lymph node metastasis. Multifocality was defined as more than one cancer focus in the ipsilateral lobe of the primary tumor.

Statistical analysis

SPSS version 21.0 software (SPSS, Inc, Chicago, IL) was used for statistical analysis. Univariate analyses for the associations between contralateral occult carcinoma and clinic-pathologic factors were performed using Pearson's chi-square test or Fisher's exact test. Binary logistic regression test was used for multivariate analysis of statistically significant variables from the univariate analysis. Statistical significance was defined as a P value less than 0.05.

Results

According to the inclusion criteria, a total of 300 patients with unilateral PTC were enrolled in our study, consisting of 62 males and 238 females, with an average age of 48.87±11.54 years. All patients underwent total thyroidectomy plus ipsilateral or bilateral central lymph node dissection (level VI). Lateral neck lymph node dissection (level II, III, IV and V) was performed in 55 (18.3%) patients. Hashimoto's thyroiditis was found in 50 (16.7%) patients. "Benign" nodules in the contralateral lobe were detected in 266 (88.7%) patients by preoperative US. The incidence of capsular invasion and extrathyroidal extension was 53.3% (160/300) and 8.3% (25/300), respectively. The rate of central and lateral cervical lymph node metastasis was 36.0% (108/300) and 18.3% (55/300), respectively. The rate of cervical lymph node metastasis in patients with primary tumor size ≤1 cm and >1 cm was 29.1% (60/206) and 66.0% (62/94), respectively

Table 2. Univariate analysis: clinic-pathologic factors in relation to contralateral occult carcinoma in 300 unilateral PTC patients

Demographic characteristics	Negative contralateral occult carcinoma (n=245)	Positive contralateral occult carcinoma (n=55)	*P* value
Mean of Age (year)	49.19±11.34	47.45±12.44	0.314
≤45	74	21	0.250
>45	171	34	
Gender			
Male	46	16	0.088
Female	199	39	
Hasimoto's Thyroiditis			
No	202	48	0.386
Yes	43	7	
Contralateral Nodules			
No	28	6	0.913
Yes	217	49	
Nodule size in the contralateral lobe by US (cm)	0.97±1.04	1.11±1.13	0.385
<0.5	81	18	0.574
0.5-1	91	17	
>1	73	20	
Primary tumor size by US (cm)	1.22±0.94	1.54±1.34	0.101
≤1	140	29	0.551
>1	105	26	
Multifocality of Primary Tumor			
No	199	27	0.000
Yes	46	28	
Primary Tumor Size by Pathology (cm)	0.98±0.76	1.14±1.17	0.355
≤0.5	87	21	0.709
0.5-1	82	16	
>1	76	18	0.805
Capsular Invasion			
No	112	28	0.485
Yes	133	27	
ETE			
No	222	53	0.261
Yes	23	2	
C-LNM			
No	161	31	0.192
Yes	84	24	
I-LNM			
No	201	44	0.724
Yes	44	11	

Abbreviations: US, ultrasonography; ETE, extrathyroidal extension; c-LNM, central lymph node metastasis; l-LNM, lateral lymph node metastasis.

(*P*=0.000). The proportion of patients with occult contralateral carcinomas was 18.3% (55/300). In patients with contralateral occult carcinoma, the median size of primary tumor and occult contralateral tumor was 0.7 cm (range, 0.2-7.0 cm) and 0.2 cm (range, 0.1-0.7 cm), respectively. Of the 55 patients with occult contralateral carcinoma, 7 (12.7%) cases were complicated with Hashimoto's thyroiditis, 49 (89.1%) with contralateral "benign" nodules, 28 (50.9%) with mulifocality of primary tumor, 27 (49.1%) with capsular invasion, 2 (3.6%) with

Table 3. Multivariate logistic regression analysis of the risk factors of contralateral occult carcinoma in 300 patients with unilateral PTC

Variables	B (SE)	*P* value	Exp (β)	95% CI Exp (β)	
				Lower	Upper
Multifocality	1.501 (0.315)	0.000	4.486	2.418	8.325
Constant	-1.997 (0.205)				

Abbreviations: β, beta; SE, standard error; Exp (β), odds ratio; CI, confidence interval.

extraglandular extension, 24 (43.6%) with ipsilateral central lymph node metastasis, and 11 (20.0%) with lateral neck lymph node metastasis (**Table 1**).

The univariate analysis revealed that the rate of contralateral occult carcinoma was significantly increased in patients with the presence of multifocality in primary tumor (37.8% vs. 11.9%, *P*=0.000) (**Table 2**). In multivariate analysis, the multifocality of primary tumor was an independent risk factor for contralateral occult carcinoma in patients with unilateral PTC (*P*=0.000, *odds ratio*=4.486) (**Table 3**).

Discussion

The optimal treatment of unilateral PTC has been controversial, and the principle of domestic and foreign experts has gradually become the consensus of individualized treatment according to prognostic factors of tumor. Bilimoria *et al.* demonstrated that total thyroidectomy resulted in lower recurrence rates and improved survival for PTC ≥1 cm compared with lobectomy, with no impact on recurrence or survival for PTC <1 cm [6]. After a long-term follow-up, Noguchi *et al.* reported that total thyroidectomy was unnecessary for papillary thyroid microcarcinoma (PTMC) even it could be fatal [7]. Based on the guidelines of American Thyroid Association (ATA), total thyroidectomy was recommended for thyroid cancer with a diameter greater than 1 cm, the contralateral nodules, regional or distant metastasis, history of head and neck radiotherapy, and family history of differentiated thyroid cancer [8]. The optimal extent of surgical resection in cases with preoperative unilateral PTMC remains a topic of debate.

In previous literatures, the incidence of occult carcinoma in the contralateral lobe of thyroid was 13-56% [1, 3-5]. In our study, the incidence of contralateral occult carcinoma was 18.3% (55/300). Therefore, more attention should be paid to the presence of contralateral occult carcinoma in patients with unilateral PTC. In this study, there was no significant association between clinic-pathological characteristics (e.g. age, gender, primary tumor size, capsule invasion, extraglandular extension and lymph node metastasis) and contralateral occult carcinoma (**Table 2**), which was consistent with previous literature reports [4, 9, 10].

One approach to deciding which patients with preoperative unilateral PTC should receive total thyroidectomy is the use of ultrasound imaging to make sure the contralateral lobe with evident disease. Ultrasound characteristics with respect to malignancy include microcalcifications, hypoechoic features, increased nodular vascularity, infiltrative margins, and nodules that appear taller than wide on transverse view [11]. Lee *et al.* asserted that the presence of a probably benign nodule in the contralateral lobe by preoperative US occurred in 71.8% of patients with occult contralateral carcinoma and it was an independent predictive factor for contralateral occult carcinoma in patients with unilateral PTMC [12]. In the present study, there were 266 (88.7%) patients with "benign" nodules in the contralateral lobe by preoperative US, and 18.4% (49/266) were confirmed with contralateral occult microcarcinoma by pathology. Of 34 patients with absence of obvious nodules in the contralateral lobe, 6 (17.6%) cases were eventually diagnosed with occult PTMC. However, our results revealed that the presence of contralateral "benign" nodules by preoperative US was not associated with the presence of contralateral occult carcinoma (*P*=0.913).

The rate of missed lesions in contralateral lobe was 4.7% for PTCs and 5.5% for PTMCs by the preoperative evaluation [10]. In a previous study, the rate of PTC misdiagnosis as a benign nodule on US and FNA was reported as 3.9% [13]. Therefore, the association between preoperative US features and the presence of occult contralateral carcinoma was important in order to determine which patients with preoperative unilateral PTC should receive total thyroidectomy. However, our results showed that the pres-

ence of occult contralateral carcinoma appeared to be unrelated to the size of primary tumor or nodules in the controlateral lobe by preoperative US. This result may be caused by the inaccurate location of occult malignant nodule by US as multiple lesions in controlateral lobe. Moreover, the occult carcinoma sometimes belonged to a small proportion of the "benign" nodules in the contralateral lobe and the actual size could not be measured by preoperative US. However, considering to the probable multiple lesions in the contralateral lobe and the difficulty of intraoperative location by frozen section, total thyroidectomy was usually performed for patients with unilateral thyroid carcinoma concomitant with contralateral nodules [14].

The relationship between the size of primary tumor by pathology and the presence of contralateral occult carcinoma remains controversy [4, 10]. In the present study, the rate of occult contralateral carcinoma in patients with primary tumor size ≤0.5 cm, 0.5-1.0 cm and >1 cm, was 19.4% (21/108), 16.3% (16/98), and 19.1% (18/94), respectively. The incidence of occult contralateral carcinoma had no difference between patients with primary PTC >1 cm and those ≤1 cm (19.1% vs. 18.0%, *P*=0.805) as same between patients with primary PTMC >0.5 cm and those ≤0.5 cm (16.3% vs. 19.4%, *P*=0.709). These results demonstrated that the size of the primary tumor by pathology could not predict the risk of the contralateral occult carcinoma, which was similar to the report by Grigsby *et al.* [3]. Although this is not enough to directly recommend total thyroidectomy, patients should be fully informed the possibility of contralateral occult carcinoma before surgery.

The multifocality was defined as more than 1 tumor focus located in the ipsilateral lobe of the primary tumor [4]. As PTC has the high incidence for multiple lesions and the consequent of contralateral occult carcinoma, most surgical physicians tend to total thyroidectomy, even for PTMC [3, 15-18]. In our study, the rate of multifocality in primary tumor was 24.7% (74/300) and 37.8% (28/74) of these patients suffered contralateral occult carcinoma. Moreover, our results showed the significant association between multifocality of the primary tumor in ipsilateral lobe and occult carcinoma in contralateral lobe (37.8% vs. 11.9%, *P*=0.000). And the presence of multifocality in primary tumor was an independent predictive factor of contralateral occult carcinoma (*P*=0.000, *odds ratio*=4.486), which was similar to other previous reports [4, 9, 19]. Shattuck *et al.* noted that multifocal tumors in PTC had independent origins, which provided theoretical support for the appropriateness of bilateral thyroidectomy and radioablation of remaining tissue [20].

A major limitation of this study is the possible bias inherent in a retrospective review of a prospectively collected database. As the lack of long-term follow-up results, the prognostic implication of occult contralateral carcinomas needs to be further evaluated. As genetic or immunohistochemical biomarkers of thyroid cancer were not routinely detected, the relationship between biomolecular markers (e.g. BRAF V600E) and occult contralateral carcinomas remains uncertain.

Conclusions

In patients with unilateral PTC, there were no significant associations between clinic-pathological characteristics and contralateral occult carcinoma. However, the multifocality of primary tumor in the ipsilateral lobe was an independent predictive factor for occult carcinoma in contralateral lobe. Currently, the presence of "benign" nodules in contralateral lobe detected by preoperative US was not considered as a risk factor of contralateral occult carcinoma, which should be further tested by large series of studies. The prediction of contralateral occult carcinoma in unilateral PTC using pathological features could be useful for determining the optimal extent of surgery.

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Disclosure of conflict of interest

None.

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