

Research Article

Characteristics of contralateral carcinomas in patients with papillary thyroid microcarcinomaDebin Xu^{1, #}, Chunlei Yuan^{1, #}, Shimin Zhuang², Liangen Xie², Tianrun Liu^{2, *}¹Department of Thyroid and Neck Surgery, the Second Affiliated Hospital of Nan Chang University, China²Departments of Otolaryngology-Head & Neck Surgery, The Sixth Affiliated Hospital of Sun Yat-sen University, 26YuanChun Two Road, Guangzhou, Guangdong, 510655, People's Republic of China

Purpose: According to the ATA and NCCN guidelines (2015, USA), patients with papillary thyroid carcinoma (PTC) not less than 4 cm, especially for papillary thyroid microcarcinoma, are now eligible for lobectomy. However, the incidence of contralateral carcinomas is about 20% in some patients in papillary thyroid microcarcinoma, and such patients should receive total thyroidectomy, other than lobectomy. The purpose of this study is to characterize contralateral carcinomas in the patients with papillary thyroid microcarcinoma.

Methods: A retrospective study was performed, including 546 papillary thyroid microcarcinoma patients treated with total thyroidectomy at a single institute were enrolled from January 2008 and December 2014. Patients were divided into two groups based on contralateral. The patients with contralateral microcarcinoma were further investigated regarding the preoperative presence of the contralateral tumor.

Results: Contralateral microcarcinoma was found in 26% of papillary thyroid microcarcinoma patients. Eighty-four (66.2% of them) had a contralateral tumor detected by preoperative ultrasound. In 19 patients (13.4%), fine-needle aspiration biopsy was skipped because the contralateral tumor had benign features. In total, 18 patients (12.6 %) had suspicious features on ultrasound examination. Although 11 patients were not diagnosed with contralateral tumor preoperatively, they were finally diagnosed with contralateral microcarcinoma by postoperative pathology.

Conclusions: Contralateral cancer is found more commonly in the patients with large tumors. Therefore, total thyroidectomy may be necessary for patients with multifocal or/and large tumors. 7.7 % of the patients were false negatively diagnosed without contralateral cancer before the tumor biopsy.

Keywords: Papillary thyroid microcarcinoma; Contralateral carcinoma; Surgical strategy.

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Introduction

Papillary thyroid microcarcinoma (PTMC) is defined as a papillary thyroid carcinoma measuring 1.0 cm or less in maximal diameter [1]. With the widespread use of thyroid ultrasound (US) and US-guided fine-needle aspiration biopsy (US-FNAB), the diagnosis rate of PTMC has been increased remarkably [2]. In the past, most patients with PTMC were diagnosed from specimens of thyroid removed from benign diseases, such as Graves' disease, follicular adenoma, and multinodular goiter. Although PTMC is usually associated with a favorable prognosis, there is an ongoing debate about the management of PTMC. Generally, clinicians choose simple lobectomy or total thyroidectomy with or without lymph node dissection. When the surgeon decides to perform lobectomy, the possibility of contralateral cancer must be considered. The true incidence of contralateral PTMC that is not detected preoperatively but is diagnosed pathologically is unknown. Traditional arguments for adhering to total thyroidectomy are the

presence of contralateral carcinomas, the ability to perform RAI and the use of thyroglobulin as a follow-up marker with high-risk PTMC. Supporters of total thyroidectomy argue that contralateral carcinomas could affect disease recurrence and survival rates [3-5]. Interestingly, this argument is mainly based on patients with PTMC; however, the data on the incidence of contralateral carcinomas in PTMC is currently very limited [4, 5]. The aim of this study is to determine the incidence of contralateral PTMC and analyze their characteristics. Also, we determined how many patients with contralateral PTMC were missed preoperatively.

Patients and methods

We conducted a descriptive and retrospective study. Patients who underwent a total thyroidectomy for PTMC between January 2008 and December 2014 and aged ≥ 18 years were included, a total of 546 patients with PTMC who were treated by total thyroidectomy at a single institution.

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The specimens were routinely sectioned every 3 mm. One pathologist made all of the histological diagnosis based on WHO recommendations. All patients underwent preoperative US evaluation for contralateral carcinomas. The data was retrospectively analyzed with multiple variables, such as age, sex, central node metastasis, lymphovascular invasion, capsular invasion, extra thyroidal extension, multifocality, and contralateral. Multi-focality was defined as more than one cancer focus in the ipsilateral lobe of the primary cancer. Contralateral carcinomas were defined as tumors existing in both thyroid lobes. Contralateral carcinoma was diagnosed by preoperative US-FNAB or in the postoperative pathology report. Contralateral PTMC were divided into preoperatively confirmed, suspicious, and missed PTMC. We confirmed that the contralateral PTMC by preoperative FNAB. When patients had bilateral suspicious nodules on their first visit, they underwent FNAB of both lobes. When patients were already diagnosed with ipsilateral PTMC, they underwent US on the contralateral lobe to detect any contralateral tumor. When patients had a suspicious nodule in the unilateral lobe, they underwent FNAB of the lobe and US to look for a contralateral tumor. A surgeon performed all the procedures.

Suspicious US features were defined as hypoechogenicity, microcalcification, increased central vascularity, infiltrative margins, and greater height than width in the transverse plane. Because most of the patients with contralateral nodules were supposed to undergo total thyroidectomy regardless of the results, FNAB was skipped. PTMC not detected preoperatively were defined as “missed PTMC.”

To identify differences between groups for the clinicopathologic features, we used χ^2 analysis, Fisher’s exact test, and binary logistic regression tests. A *p* value < 0.05 was considered to represent statistical significance.

Table 1. Clinicopathologic features for the two tumor groups with papillary thyroid microcarcinoma, by contralateral

Characteristics	Contralateral		<i>P</i>
	Positive (n=142)	Negative (n=404)	
Age (mean, years)	48	47	
Age group			
< 45 years	58	199	0.58
≥ 5 years	84	205	
Gender			
Female	79	216	0.45
Male	63	188	
Central lymph node metastasis	45	134	0.31
Capsule invasion	34	106	0.28
Extrathyroidal extension	23	44	0.22
Lymphovascular invasion	33	41	0.21
Tumor size			
≤ 5mm	35	98	0.01
> 5mm	107	306	

Results

During the study period, 546 patients underwent total thyroidectomy. Among them, 142 (26 %) had contralateral PTMC. Clinical characteristics of the contralateral and non-contralateral groups of PTMC were shown in Table 1. No significant difference between the groups was observed in age, gender, central node metastasis, capsule invasion, extrathyroidal extension, or lymphovascular invasion. But the tumor size was significantly associated with contralateral PTMC (*P* < 0.01). On multivariate analysis, tumor size based on 5mm and multifocality showed statistical significance with regard to contralateral of PTMC (Table 2).

Table 2. Multivariate analysis of association between contralateral and other factors

Factor	RR	<i>P</i>	95 % CI
Age	1.096	0.742	0.646-1.862
Gender	1.416	0.224	0.734-3.614
Tumor size	1.720	0.042	1.046-2.826
Capsule invasion	0.586	0.582	0.342-1.456
Extrathyroidal extension	1.812	0.141	0.872-3.621
Central lymph node metastasis	0.824	0.442	0.471-1.432
Lymphovascular invasion	1.082	0.786	0.622-1.854

Of the 142 patients with contralateral PTMC, 94 (66.2 %) had a contralateral tumor detected by preoperative US. In 19 patients (13.4 %) FNAB was skipped because the contralateral tumor had benign features. 18 patients (12.6 %) had suspicious features on US examination. Finally, 11 patients diagnosed as having contralateral PTMC by postoperative pathologic (Table 3). They were counted 7.7 % of the total patients with contralateral PTMC.

Discussion

The proper extent of surgery for PTMC has been debated. Consensus guidelines recommend total thyroidectomy for patients with preoperatively detected bilateral PTMC [7]. However, the treatment of PTMC is still controversial. There are some indications for total thyroidectomy, but these indications are not absolute. They include large size (usually ≥1cm), extrathyroidal extension, lymph node metastasis, presence of a contralateral tumor, and advanced age (>45 years). Despite these indications, total thyroidectomy is usually performed more often than lobectomy in our institute because of the risk of recurrence. It also provides the opportunities to give radioactive iodine therapy, address the possibility of contralateral cancer, and follow up the thyroglobulin levels. The rate of contralateral carcinomas is in agreement with current literature that reported rates between 17 and 43%. Most of these studies focused on contralateral carcinomas in PTMC [6, 8–10], or

had limited number of patients, or failed to report clear in- and exclusion criteria, or excluded patients with follicular thyroid carcinoma [11, 12]. In contrast, our study investigated contralateral carcinoma in a large, well-described, and clinically relevant cohort, in which primary tumors were PTMC.

Table 3. Rate of preoperative diagnosis of contralateral cancer in patients with bilateral papillary thyroid microcarcinoma

Preoperative diagnosis of cPTMC	Preoperative contralateral tumor presence	Absence	Total
Confirmed	94 ^a	N/A	94
Benign/missed	19 ^b	11 ^c	30
Suspicious ^d	18	N/A	18
Total	131	11	142

a. Rate compared to the total 75 patients with cPTMC
 b. These patients had clinically benign nodules in the contralateral lobe
 c. These are missed PTMC that were not detected preoperatively
 d. Suspicious sonographic features were defined as hypoechoicity, microcalcification, increased central vascularity, infiltrative margins, and alarger height than width in the transverse plane

We performed preoperative US on patients with PTMC to detect the presence of a contralateral tumor. Although lobectomy was performed in a few patients with a contralateral benign tumor, most of the patients with a contralateral tumor regardless of malignancy underwent total thyroidectomy. Some of these patients underwent FNAB to confirm the diagnosis of contralateral PTMC before surgery. Others with suspicious sonographic findings underwent total thyroidectomy without FNAB preoperatively. The patients with a sonographically benign nodule in the contralateral lobe also did not undergo FNAB. Even with preoperative US, however, a small PTMC can be missed. In this study, the rate of missed diagnosis is 7.7 % for PTMC.

PTMC is an importance clinical issue, but contralateral lobe miss diagnosis is another clinic problem. Baudin et al found that the extent of surgery and multifocal PTMC were prognostic factors [13]. PTMC with multifocality and tumor size >0.8 cm may be associated with a more aggressive course [14]. In cases of PTMC with high risk, total thyroidectomy can be considered the proper treatment. However, contralateral cancer should be considered when a surgeon contemplates lobectomy. In particular, it is important that the final pathologic result shows contralateral for preoperative unilateral PTMC.

Pitt et al reported that the rate of contralateral cancer was 26 % for PTMC [15]. They demonstrated that the rate of contralateral PTMC was independent of the primary tumor size, and multifocal disease in the ipsilateral lobe of the primary tumor was a significant risk factor for a contralateral tumor. Koo et al. [11] found that 16 % of the 132 patients with clinically unilateral PTMC had occult contralateral carcinoma. They reported that occult contralateral papillary carcinoma was significantly more frequently occurred in patients with multifocality of the primary carcinoma in the unilateral lobe. In addition, they reported that the presence of a benign nodule in the

contralateral lobe was a predictive factor for bilaterality. Mazeh et al. [16] observed that the rates of multifocality and bilaterality in patients with PTMC were identical to those in patients with PTC >1 cm. Therefore, they suggested that total thyroidectomy is required for all patients with PTMC.

Conclusion

Contralateral was seen in 26 % of PTMC. Multifocality can help predict the possibility of bilaterality. The rates of PTMC missed in the contralateral lobe were 7.7 % for contralateral PTMC preoperatively. These rates are not high enough to indicate total thyroidectomy for treatment of PTMC. However, total thyroidectomy maybe necessary for patients with the mentioned risk factors and it should be kept in mind that the presence of contralateral cancer was missed in 7.7 % of patients with preoperatively unilateral PTMC.

Disclosure of conflict of interest

None.

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