

Original Article

Multicentric papillary thyroid carcinoma: a clinical analysis of 221 patients

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Abstract: Objective: To analyze the clinical characteristics of patients with multicentric papillary thyroid carcinoma and provide a reference to determine the necessity of total thyroidectomy during treatment. Methods: We conducted a retrospective analysis of the clinical characteristics of 221 treatment-naïve patients with multicentric papillary thyroid carcinoma treated at our department. We analyzed the clinical characteristics of these two groups and performed univariate and multivariate analyses to investigate the distribution pattern and influencing factors of the lesions of multicentric papillary thyroid carcinoma. Results: This study showed that the incidence of multicentric papillary thyroid carcinoma was 21.7% (221/1017), of which 62.0% (137/221) of the cases were bilateral. The univariate analysis showed that the risk factors for a lesion in the contralateral lobe in patients with unilateral multicentric papillary thyroid carcinoma included gender (male; $P = 0.002$), ≥ 3 lesions ($n = 3$ and $n \geq 4$; $P < 0.001$), and total lesion diameter ≥ 4 cm ($P = 0.001$). The multivariate analysis showed that ≥ 3 lesions ($n = 3$ and $n \geq 4$; $P < 0.001$) and total lesion diameter ≥ 4 cm ($P = 0.002$) were independent predictors for a lesion in the contralateral lobe in patients with unilateral multicentric papillary thyroid carcinoma. Conclusion: A total thyroidectomy is necessary for patients with multicentric papillary thyroid carcinoma, regardless of unilateral or bilateral involvement.

Keywords: Multicentric, papillary thyroid carcinoma, total thyroidectomy

Introduction

Multicentric lesions are one of the common features of papillary thyroid carcinoma. The reported incidence of multicentric papillary thyroid carcinoma is 18%-87% [1-6]. Previously, clinicians have been less concerned about multicentric lesions in the study and treatment of papillary thyroid carcinoma, and no detailed description was provided in the 2012 National Comprehensive Cancer Network (NCCN) guidelines. One possible explanation for this is that the overall prognosis for treating papillary thyroid carcinoma is good, and the 10-to-15-year survival rate is $\geq 90\%$. However, the long-term survival is no longer the only objective that clinical specialists and patients are concerned about, as the potential psychological and physical risks due to residual or recurrent cancer and subsequent surgeries deserve equal atten-

tion. In addition to performing each surgery successfully according to standard procedures, it is important to better understand the clinical characteristics of papillary thyroid carcinoma. In recent years, researchers worldwide have conducted studies on the multicentric nature of the lesions of papillary thyroid carcinoma but have different opinions regarding their understanding and treatment strategies for this condition. The main controversies include 1) whether multicentric lesions observed in papillary thyroid carcinoma are multiple tumor lesions that develop at the same time or one single lesion disseminating from the thyroid [3, 6-8] and 2) the necessity of a total thyroidectomy for multicentric papillary thyroid carcinoma [9, 10].

In this study, we conducted a retrospective analysis of the case data of patients with multicentric papillary thyroid carcinoma treated at

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Table 1. Clinical characteristics of 221 patients with multicentric papillary thyroid cancer

Factor		n	%
Gender	M	84	38.0
	F	137	62.0
Age (Years)	< 45	146	66.1
	≥ 45	75	33.9
Number of lesions	2	159	72.0
	3	29	13.1
	≥ 4	33	14.9
Lesion site	Unilateral involvement	84	38.0
	Bilateral involvement	137	62.0
Total lesion diameter (cm)	< 1	18	8.1
	≥ 1, < 4	104	47.1
	≥ 4	99	44.8
Extraglandular involvement	Y	25	11.3
	N	196	88.7
Micro-cancer	Y	32	14.5
	N	189	85.5
Concurrent Hashimoto's thyroiditis	Y	35	15.8
	N	186	84.2
Local recurrent/residual lesions	N	200	90.5
	Primary lesion	6	2.7
	Lymph node	15	6.8
Distant metastasis	N	217	97.8
	Y	5	2.2
Death	N	215	97.3
	Y	7	3.9

the Department of Head and Neck Surgery, Sun Yat-sen University Cancer Center. The aim was to further understand the multicentric nature of primary lesions and the characteristics and pattern of cervical lymph node metastasis to help surgeons improve their understanding of multicentric papillary thyroid carcinoma and provide a basis for targeted improvement of the treatment of this disease, thereby achieving the goal of individualized treatment.

Materials and methods

Case data

The 221 cases of multicentric papillary thyroid carcinoma were selected from a database of 1,017 treatment-naïve patients with papillary thyroid carcinoma treated at the Department of Head and Neck Surgery, Sun Yat-sen University Cancer Center from January 2001 to November 2010. Patients who underwent a partial thy-

roidectomy at another hospital and were later transferred to our hospital for further treatment were excluded from this study. All cases of papillary thyroid carcinoma and their multicentric characteristic were confirmed by a postoperative pathological examination.

Before surgery, the patients underwent a physical examination, thyroid computed tomography (CT), and Doppler-ultrasound of the thyroid and cervical lymph nodes for an overall assessment of thyroid lesions and cervical lymph nodes. Moreover, Doppler ultrasound-guided fine needle aspiration was performed for cytological analysis, or intraoperative pathological examination of frozen specimens was performed to confirm papillary thyroid carcinoma and determine lateral cervical lymph node metastasis. Based on the characteristics of the primary lesions, 135 patients (61.1%) underwent a total thyroidectomy, 16 (7.2%) underwent a subtotal thyroidectomy, and 70 (31.7%) underwent resection of one lobe + the isthmus. The indications for a

total thyroidectomy included age < 15 or ≥ 45 years, a history of radiation, significant extracapsular involvement, a tumor diameter > 4 cm, and bilateral lesions. Patients who did not meet these criteria underwent resection of one lobe + the isthmus (and subtotal resection if the lesion in the contralateral lobe was benign). All 221 patients underwent central lymph node dissection, and those with positive pathology for lateral neck lymph nodes also underwent therapeutic lateral neck lymph node dissection (region II-V and region I in cases of positive lymph nodes, unilateral dissection in 93 cases [42.1%] and bilateral dissection in 47 cases [21.3%]).

Statistical analysis

SPSS 13.0 (SPSS Inc., Chicago, IL, USA) was used for the statistical analysis. A χ^2 test was performed for the univariate analysis; the logis-

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Table 2. Clinical characteristics of 45 patients with unilateral multicentric papillary thyroid cancer and a lesion in the contralateral lobe

Factor		n	%
Gender	M	25	55.6
	F	20	44.4
Age (Years)	< 45	27	60.0
	≥ 45	18	40.0
Number of lesions	2	9	20.0
	3	18	40.0
	≥ 4	18	40.0
Total lesion diameter (cm)	< 1	0	0
	≥ 1, < 4	21	46.7
	≥ 4	24	53.3
Micro-cancer	Y	7	15.6
	N	38	84.4
Extraglandular involvement	Y	8	17.8
	N	37	82.2

tic regression model was used for the multivariate analysis. A value of $P < 0.05$ was considered statistically significant.

Results

Clinical characteristics of 221 patients with multicentric papillary thyroid carcinoma

As shown in **Table 1**, the incidence of multicentric papillary thyroid carcinoma was 21.7% (221/1017). The median age was 44 (7-105) years; 84 patients were male, and 137 patients were female (male:female ratio, 2:3). Postoperative pathological reports were used to determine the number of lesions, sites, and total lesion diameter (the sum of the maximum diameter of each lesion) in each patient (**Table 1**). The results showed that 62.0% of the cases (137/221) were bilateral; for patients with unilateral multicentric papillary thyroid carcinoma, 34.9% (45/129) had a lesion in the contralateral lobe. Moreover, 35 patients (15.8%) also had Hashimoto's thyroiditis. All patients were followed up through October 2013, with a median follow-up time of 5.0 years; 21 patients (9.5%) had local recurrence, including six cases (2.7%) of recurrence of primary lesions and 15 cases (6.8%) of recurrence of cervical lymph nodes; five patients (2.2%) had distant lung metastases, and seven patients (3.9%) died of disease-related causes.

Clinical characteristics of 45 patients with unilateral multicentric papillary thyroid carcinoma with lesions in the contralateral lobe

Among the 221 patients with multicentric papillary thyroid carcinoma, 129 cases were unilateral, of which, 34.9% (45/129) exhibited lesions in the contralateral lobe. The clinical characteristics of the 45 patients with unilateral multicentric papillary thyroid carcinoma with lesions in the contralateral lobe are shown in **Table 2**.

A χ^2 test was performed for univariate analysis of the 129 patients with unilateral multicentric papillary thyroid carcinoma, and the results showed that the risk factors for lesions in the contralateral lobe in these patients included gender (male; $P = 0.002$), ≥ 3 lesions ($n = 3$ and $n \geq 4$; $P < 0.001$), and total lesion diameter ≥ 4 cm ($P = 0.001$), while age ($P = 0.372$), micro-cancer ($P = 0.272$), and extraglandular involvement ($P = 0.111$) were irrelevant (**Table 3**).

A logistic regression model was used for multivariate analysis of 129 patients with unilateral multicentric papillary thyroid carcinoma, and the results showed that ≥ 3 lesions ($n = 3$ and $n \geq 4$; $P < 0.001$) and total lesion diameter ≥ 4 cm ($P = 0.002$) were independent factors for a lesion in the contralateral lobe in these patients (**Table 4**).

Features of cervical lymph node metastasis in 221 patients with multicentric papillary thyroid carcinoma

As shown in **Table 5**, the overall incidence of cervical lymph node metastasis in 221 patients with multicentric papillary thyroid carcinoma was 79.6% (176/221), the incidence of lateral cervical lymph node metastasis was 63.4% (140/221), and the incidence of central lymph node metastasis was 64.3% (142/221), which were significantly higher than the values of the overall group (1,017 patients with papillary thyroid carcinoma; 51.3%, 40.9%, and 40.7%, respectively) and those of the 796 patients with single-lesion papillary thyroid carcinoma (43.5%, 34.7%, and 34.2%, respectively) from January 2001 to November 2010. In addition, for patients with multicentric papillary thyroid carcinoma who had positive central lymph nodes, the incidence of lateral cervical lymph node metastasis was 78.9% (112/142).

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Table 3. Univariate analysis of the relevant factors for a lesion in the contralateral lobe in 129 patients with unilateral multicentric papillary thyroid cancer

Factor	n	Contralateral lesion		P value
		Y	N	
Gender	M	48	25	0.002
	F	81	20	
Age (Years)	< 45	84	27	0.372
	≥ 45	45	18	
Number of lesions	2	70	9	0.000
	3	29	18	
	≥ 4	30	18	
Total lesion diameter (cm)	< 1	15	0	0.001
	≥ 1, < 4	68	21	
	≥ 4	46	24	
Micro-cancer	Y	27	7	0.272
	N	102	38	
Extraglandular involvement	Y	15	8	0.111
	N	114	37	

Table 4. Multivariate analysis for a lesion in the contralateral lobe in patients with unilateral multicentric papillary thyroid cancer

Factor	P value	Exp (B)	95% CI
Gender (M)	0.792	0.887	0.364-2.161
Age ≥ 45 years	0.564	1.300	0.534-3.163
Number of lesions ≥ 3	< 0.001	3.205	1.886-5.448
Total lesion diameter ≥ 4 cm	0.002	3.230	1.560-6.690

Discussion

Researchers have different opinions about whether a total thyroidectomy is necessary in patients with multicentric papillary thyroid carcinoma. The 2012 NCCN guidelines and the *Guidelines for Differentiated Thyroid carcinoma* from the Thyroid Carcinoma Group, Head and Neck Branch of the China Anti-Cancer Association note that bilateral lesions and a lesion diameter > 4 cm are indications for total thyroidectomy in patients with papillary thyroid carcinoma; however, no recommendation for multicentric lesions is provided. The consensus of the European Society for Endocrine Surgeons (ESES) regarding multicentric papillary thyroid carcinoma states that for patients with multicentric papillary thyroid carcinoma after a subtotal thyroidectomy, a second thyroid dissection is necessary [11]. Mazeh et al. [9] found that multicentric and contralateral lesions are

common in papillary thyroid carcinoma, and the incidence is unrelated to the tumor size; therefore, they suggested performing a total thyroidectomy in patients with multicentric papillary thyroid carcinoma. In this paper, we will pool the results of our study with those in the literature for the discussion.

This study showed that the incidence of multicentric papillary thyroid carcinoma was 21.7% (221/1017, **Table 1**), which was consistent with the values reported in the literature (18%-87%) [1-6]. In this study, we performed statistical analyses of the sites and the number of lesions of multicentric papillary thyroid carcinoma (**Table 1**) and showed that multicentric lesions were restricted in a single lobe in 38% (84/221) of cases and were bilateral in 62% (137/221) of cases. Moreover, unilateral multicentric papillary thyroid carcinoma (with or without a lesion in the contralateral lobe) accounted for 58.4% (129/221) of the cases, and 34.9% (45/129) of these patients had a lesion in the contralateral lobe. The univariate analysis showed that (**Table 3**) gender (male; $P = 0.002$), ≥ 3 lesions ($n = 3$ and $n \geq 4$; $P < 0.001$), and total lesion diameter ≥ 4 cm ($P = 0.001$) were risk factors for the presence of a lesion in the contralateral lobe in patients with unilateral multicentric papillary thyroid carcinoma thyroid; the multivariate analysis showed that ≥ 3 lesions ($n = 3$ and $n \geq 4$; $P < 0.001$) and total lesion diameter ≥ 4 cm ($P = 0.002$) were independent predictors for a lesion in the contralateral lobe in patients with unilateral multicentric papillary thyroid carcinoma thyroid (**Table 4**). These results showed that the incidence of multicentric lesions is high in papillary thyroid carcinoma patients, and the incidence of bilateral involvement is higher than that of unilateral involvement. A high percentage of patients (34.9%) with unilateral multicentric papillary thyroid carcinoma had a lesion in the contralateral lobe, and this was related to the number of unilateral multicentric lesions and the total lesion diameter. Therefore, we believe that a total thyroidectomy is necessary for both unilateral and bilateral multicentric papillary thyroid carcinoma.

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Table 5. Cervical lymph node metastasis in 1017 patients with papillary thyroid cancer (overall, single-lesion, and multicentric) from January 2001 to November 2010

Category	Site	n	%
Papillary thyroid cancer (n = 1017)	Overall	522	51.3
	Lateral cervical	416	40.9
	Central	414	40.7
Single-lesion papillary thyroid cancer (n = 796, 78.3%)	Overall	346	43.5
	Lateral cervical	276	34.7
	Central	272	34.2
Multicentric papillary thyroid cancer (n = 221, 21.7%)	Overall	176	79.6
	Lateral cervical	140	63.4
	Central	142	64.3

In this study, 15.8% (35/221) of the patients with multicentric papillary thyroid carcinoma also had Hashimoto's thyroiditis, while the incidence of concurrent papillary thyroid carcinoma and Hashimoto's thyroiditis was 10-58% [12, 13] in the literature. Widder believed that for patients with Hashimoto's thyroiditis, long-term antigen challenge may accelerate the development of malignant tumors [14]. Additionally, studies have found that Hashimoto's thyroiditis and papillary thyroid carcinoma share some molecular mechanisms; for example, RET/PTC rearrangement may modulate the early stages of tumorigenesis and thyroid inflammatory responses [13, 15]. Hashimoto's thyroiditis generally involves extensive lesions in the entire thyroid lobe; therefore, this disease may be one of the factors for multicentric lesions in papillary thyroid carcinoma.

Researchers have presented two opinions regarding the origin of multicentric lesions in papillary thyroid carcinoma: multiple thyroid lesions may develop at the same time and a single lesion may disseminate from the thyroid. US researchers Trisha et al. [16] used polymerase chain reaction of human androgen receptor genes to identify the inactivation pattern of the X chromosomes in each lesion of each of 17 female patients with multicentric papillary thyroid carcinoma and showed that multicentric lesions are often derived from a single lesion disseminating from the thyroid. McCarthy et al. [17] reached the same conclusion, that multicentric lesions in multicentric papillary thyroid carcinoma usually originates from a single clone, and they believed that intraglandular dissemination may play an important role in the metastasis of papillary thyroid carcinoma. The

data obtained in this study are insufficient to support any conclusion regarding the origin of multicentric lesions in papillary thyroid carcinoma; however, based on the data and results of this study, we believe that a total thyroidectomy is necessary for patients with multicentric papillary thyroid carcinoma, regardless of the origin of the multicentric lesions.

Many studies have shown that the presence of papillary thyroid carcinoma lesions with a multicentric characteristic increases the risk of lymph node metastasis, distant metastasis, postoperative occult residual lesions, and local recurrence [1, 3, 4, 6, 18].

This study (Table 5) showed that among 221 patients with multicentric papillary thyroid carcinoma, the overall incidence of cervical lymph node metastasis was 79.6% (176/221), the incidence of lateral cervical lymph node metastasis was 63.4% (140/221), and the incidence of central lymph node metastasis was 64.3% (142/221), which were significantly higher than the values of the overall group (1,017 patients with papillary thyroid carcinoma; 51.3%, 40.9%, and 40.7%, respectively) and those of 796 patients with single-lesion papillary thyroid carcinoma (43.5%, 34.7%, and 34.2%, respectively) evaluated during the same period. Kim et al. [19] showed that multicentric papillary thyroid carcinoma was more likely than single-lesion papillary thyroid carcinoma to have extraglandular involvement and cervical lymph node metastasis and that the presence of multicentric lesions was an independent predictor for recurrent or residual papillary thyroid carcinoma ($P = 0.04$). Chinese researchers conducted a retrospective analysis of 282 cases of single-lesion papillary thyroid carcinoma and 86 cases of multicentric papillary thyroid carcinoma and concluded that patients with multicentric papillary thyroid were more likely to have lymph node metastasis and vascular involvement, but they did not observe any difference in the distant metastasis and 10-year survival rate between the two groups [20]. Moreover, this study found that for patients with multicentric papillary thyroid carcinoma who had central lymph node metastasis, the incidence of lateral cervical lymph node metastasis was 78.9% (112/142). Considering the results of this study and the literature reports, we believe that patients with multicentric papillary thyroid carcinoma are prone to

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cervical lymph node metastasis, and thus we recommend routine prophylactic central lymph node dissection and close monitoring of lateral cervical lymph nodes. An intraoperative lateral cervical lymph node biopsy should be performed if cervical lymph node metastasis is suspected before surgery.

Both this study and the literature reports have shown that patients with multicentric papillary thyroid carcinoma are prone to cervical lymph node metastasis, which, as suggested by some recent studies, may affect the prognosis of certain patients [21-24]. However, the treatment outcome detailed in **Table 1** shows that among 221 patients with multicentric papillary thyroid carcinoma, the incidence of recurrent or residual lesions, the distant metastasis rate, and the survival rate were 9.5%, 2.2%, and 97.3%, respectively, with no significant difference from the overall prognosis of patients with papillary thyroid carcinoma. In this study, the median follow-up time was 5.0 years, and this relatively short follow-up time may contribute to the lack of significant results. Hence, this study lacked the statistical power to indicate the effect of multicentric lesions on local recurrence/residual lesions and the long-term survival of patients with papillary thyroid carcinoma. Nevertheless, we will continue to follow the patients included in this study to further investigate the clinical characteristics and prognosis of multicentric papillary thyroid carcinoma.

Conclusion

In short, we believe that the incidence of multicentric papillary thyroid carcinoma is relatively high; bilateral involvement is more common than unilateral involvement. For patients with unilateral multicentric thyroid papillary cancer, the probability of having a lesion in the contralateral lobe is high, which is related to the number of unilateral multicentric lesions and the total lesion diameter. Thus, a total thyroidectomy is necessary for multicentric papillary thyroid carcinoma, regardless of either unilateral or bilateral involvement or the origin of the multicentric lesions (multiple lesions developing at the same time or a single lesion disseminating from the thyroid). Moreover, patients with multicentric papillary thyroid carcinoma are prone to cervical lymph node metastasis, and thus we recommend routine prophylactic central lymph

node dissection and the close monitoring of lateral cervical lymph node metastasis.

Disclosure of conflict of interest

None.

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