

Original Article

Clinical characteristics and surgical resection of multifocal papillary thyroid carcinoma: 168 cases

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Abstract: Purpose: To investigate clinical characteristics and surgical treatment of multifocal papillary thyroid carcinoma. Methods: A total of 648 patients diagnosed with papillary thyroid carcinoma were enrolled, 168 with multifocal papillary thyroid carcinoma. Clinicopathological factors including gender, age at diagnosis, family history of thyroid tumor, multiplicity and bilaterality of tumor, extra-thyroidal extension, lymph node involvement and other factors were statistically compared. Results: The incidence of multifocal papillary thyroid carcinoma was 25.9% and 117 presented with bilateral thyroid gland lesions. In multifocal group, patients had a higher ratio of male subjects, family history of thyroidal tumor, neck lymph node metastasis and extra-thyroidal extension by B-ultrasound. Solitary papillary thyroid carcinoma tended to be with a higher rate of benign goiters. In multifocal group, males with neck lymphadenectomy, ≥ 3 tumor masses or bilaterality of tumors tended to present with larger tumors, a higher incidence of neck lymph node metastasis and extra-thyroidal extension. 164 cases completed the follow-up, 5 died, 1 suspected with lung metastasis and still survived, 6 underwent repeated surgery due to lymph node recurrence at 3-41 months postoperatively and 2 surgically treated with recurrent gland tumor. Overall 1-, 2-, 5-, and 10-year survival rate was 98.2%, 97.4%, 96.5% and 96.5%, respectively. Conclusion: Multifocal papillary thyroid carcinoma is more malignant and highly differentiated than solitary lesions. Total thyroidectomy combined with neck dissection of central compartment could be utilized as standard treatment. Lateral nodular dissection should be considered for the patients with lymph node metastasis.

Keywords: Thyroid tumors, thyroidectomy, neck lymph node dissection, papillary carcinoma

Introduction

Thyroidal cancer is the most common endocrine-related malignant tumor. Multifocal papillary thyroid carcinoma is equally relatively common in clinical practice [1, 2]. This study retrospectively evaluated the clinical data of 648 patients who were pathologically diagnosed with papillary thyroid carcinoma and underwent surgery in our hospital for the first time from January 2000 to December 2011 (168 of whom showing multifocal papillary thyroid carcinoma), aiming to investigate the clinical characteristics and surgical approach in treatment of multifocal papillary thyroid carcinoma.

Materials and methods

General data

Among 168 patients with multifocal papillary thyroid carcinoma, 49 (29.2%) were male and

119 (70.8%) were female, aged 42 ± 4.1 years (range from 14 to 78 years). A total of 114 patients (67.9%) presented with neck masses as the primary symptom. Physical examination revealed 38 cases (22.6%) with neck masses, 6 (3.6%) neck lymph node enlargement, 1 (0.6%) hoarseness and nine (3.9%) with alternative symptoms. Upon admission, physical examination indicated palpable lymph node enlargement in 18 cases. Prior to surgery, 156 patients underwent B-ultrasound of the thyroid gland, 71 (45.5%) among whom presenting with neck lymph node enlargement and 101 (64.7%) showing signs of calcified lymph nodular lesions. In total, 137 patients received thyroid function test, identifying that the serum level of thyroid stimulating hormone (TSH) was higher than normal value in 12 cases. Preoperative examination detected distal metastasis involving lung, bone and adrenal in 2 patients.

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Table 1. Comparison of clinicopathological characteristics between multifocal and solitary groups (n)

Parameters	Multifocal group (n = 168)	Solitary group (n = 480)	χ^2 or F value ^a	P value
Gender				
Male	49	89	8.382	0.004
Female	119	391		
Mean age (year)	42.2 ± 12.2	43.5 ± 12.7	1.190	0.235
Family history of malignant tumor				
Yes	8	7	4.634	0.031
No	160	471		
Neck lymph nodular enlargement by physical examination ^b				
Yes	18	14	16.344	0.000
No	148	464		
TSH level elevation				
Yes	12	19	2.500	0.114
No	125	360		
Lymph nodular enlargement by B-ultrasound				
Yes	71	139	11.531	0.001
No	85	232		
Nodular calcified lesions				
Yes	101	223	11.544	0.001
No	55	232		
Maximum diameter of a tumor (mm)	17.3 ± 13.0	15.7 ± 12.7	1.343	0.180
Complicated with benign thyroidal diseases ^b				
Yes	69	287	17.616	0.000
No	99	193		
Neck lymph nodular metastasis				
Yes	59	118	6.958	0.008
No	109	362		
Extra-thyroidal involvement				
Yes	19	20	11.225	0.001
No	149	460		

Note: ^aDenotes mean age and maximum diameter of a tumor (F value), χ^2 for other parameters; ^bdenotes thyroid.

Subsequent follow-up

The follow-up was conducted in the patterns of paying a visit, making telephone calls or the most recent outpatient visit and medical records. The death of patients or the time of final follow-up was regarded as the endpoint of the follow up. The follow-up was concluded until December 31, 2012.

Statistical analysis

SPSS 14.0 statistical software package was used for data processing. Chin-square or F tests were utilized for group comparison. Kaplan-Meier method was employed for survival estimates. Log-rank test was used to com-

pare survivals among groups. $\alpha = 0.05$ was considered as statistical significance.

Results

Surgical approach

In total, 107 patients underwent partial or total resection of the affected gland lobe plus isthmus plus contralateral side, 37 thyroidectomy, 11 bilateral subtotal thyroidectomy, 12 excision of the affected gland lobe with/without isthmus and 1 receiving subtotal resection on the affected side. A total of 84 patients underwent neck lymph node dissection including 52 receiving unilateral dissection, 5 bilateral dissection and 27 VI area dissection alone. Six

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patients were treated with palliative excision, manifested as neck trachea, esophagus, recurrent laryngeal nerve and carotid sheath widely surrounded by tumors and two patients were complicated with tumor thrombosis in internal jugular vein. Two cases presented with distal metastasis involving lung, bone and adrenal. Six patients received partial excision of the affected gland lobe plus isthmus plus contralateral side, 1 had thyroidal lobectomy, 2 bilateral subtotal thyroidectomy, 3 palliative neck nodular dissection and 1 VI zone dissection.

Surgical observations and pathological examination

In this study, 22 patients had lesions located on the left side (13 cases with 2 lesions and 9 cases with ≥ 3 lesions), 24 right side (15 with 2 lesions and 9 with ≥ 3 lesions), 5 isthmus side (4 with 2 lesions and 1 with ≥ 3 lesions) and 117 bilateral sides (67 with 2 lesions and 50 with ≥ 3 lesions). The tumor with a maximum diameter of ≤ 1 cm was defined as small carcinoma. A total of 66 patients (39.3%) had non-small carcinoma, 68 (40.5%) simple small carcinoma and 34 (20.2%) small carcinoma complicated with non-small carcinoma (20.2%). A total of 99 patients (58.9%) had 2 lesions and 69 (41.1%) ≥ 3 lesions with the maximal number of 13 lesions. In total, 69 resected samples had benign thyroid disease including 44 (26.2%) nodular Goiter, 4 (2.4%) thyroid adenoma, 12 (7.1%) Hashimoto's thyroiditis, 5 (3.0%) nodular Goiter complicated with thyroid adenoma, 3 (1.8%) hyperthyroidism and 1 (0.6%) hyperthyroidism complicated with thyroid adenoma. Fifty nine cases (35.1%) were accompanied with neck lymph nodular metastasis including 55 (32.7%) unilateral and 4 (2.4%) bilateral metastasis. Nineteen (11.3%) presented with extra-thyroidal involvement (recurrent laryngeal nerve, trachea, esophagus, jugular vein or surrounding muscles, etc).

Comparison of clinicopathological factors between multifocal and solitary groups

Compared with patients with solitary lesion, those in the multifocal group were characterized with a higher ratio of clinicopathological factors including male ($P = 0.004$), a family history of malignant thyroid tumors ($P = 0.031$), neck lymph node enlargement detected by physi-

cal examination ($P = 0.000$) and B-ultrasound ($P = 0.001$), nodular calcified lesions ($P = 0.001$), neck nodular metastasis ($P = 0.008$) and extra-thyroidal involvement ($P = 0.001$), etc.

The incidence of patients complicated with benign thyroid disease in the solitary group was significantly higher than that in the multifocal group ($P = 0.000$). No statistical significance was observed between two groups in terms of age ($P = 0.235$), TSH level ($P = 0.114$) and maximum diameter of a tumor ($P = 0.180$), etc, as illustrated in **Table 1**.

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Male patients with neck lymph node enlargement, bilateral tumors and ≥ 3 lesions were incline to relatively high degree of malignancy and were characterized with a relatively high incidence of large tumors, neck lymph node metastasis or extra-thyroidal involvement. Those complicated with benign thyroid diseases presented with a relatively low degree of malignant multifocal papillary thyroid carcinoma (**Table 2**). Patients with a family history of thyroid cancer had a relatively younger age of onset (31.0 ± 10.7 vs 42.7 ± 12.0 , $\chi^2 = 7.338$, $P = 0.007$). Neck lymph node metastasis was not correlated with the maximum diameter of a tumor ($F = 2.043$, $P = 0.157$).

Clinical prognosis

All patients received adjuvant thyroxine or levothyrocine therapies postoperatively and 22 were treated with ^{131}I . In total, 164 patients (97.6%) were followed up. The mean follow-up duration was 46 months (range: 2-127 months). Among 6 cases receiving palliative excision, 5 patients died from apnea ($n = 3$), systemic metastasis complicated with failure ($n = 1$) and unknown causes ($n = 1$) at postoperative 2, 3, 6, 24 and 30 months. One was lost contact during follow up. Among the 159 patients, one case was suspected with pulmonary metastasis detected by chest CT scans and still survived for 16 months. During postoperative 3 to 41 months (median 12 months), 6 patients underwent repeated surgery due to neck lymph node recurrence including 5 bilateral and 1 unilateral carcinoma. Four previously received uni-

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Table 2. Comparison of clinicopathological characteristics in patients with multifocal papillary thyroid carcinoma

Parameters	Multifocal small carcinoma (n)		Maximum diameter of a tumor (mm)	Neck lymph nodular metastasis (n)		Extra-thyroidal involvement (n)	
	Yes	No		Yes	No	Yes	No
Gender							
Male	21	28	23.4 ± 17.8	22	27	11	38
Female	81	38	14.7 ± 9.4	37	82	8	111
χ^2	9.248		16.730	2.903		8.558	
<i>P</i> value	0.002		0.000	0.088		0.003	
Family history of thyroid cancer							
Yes	4	4	16.9 ± 9.0	5	3	1	7
No	98	62	17.3 ± 13.2	54	106	18	142
χ^2	0.404		0.008	2.764		0.012	
<i>P</i> value	0.525		0.931	0.096		0.931	
Neck lymph nodular enlargement by physical examination							
Yes	1	17	25.9 ± 11.5	15	3	6	12
No	100	48	16.3 ± 12.9	44	104	12	136
χ^2	25.904		8.868	20.128		10.563	
<i>P</i> value	0.000		0.004	0.000		0.001	
Lymph nodular enlargement by B-ultrasound							
Yes	38	33	19.1 ± 11.6	38	33	12	59
No	58	27	15.4 ± 11.8	16	69	4	81
χ^2	3.539		1.948	20.578		6.251	
<i>P</i> value	0.060		0.146	0.000		0.012	
Nodular calcified lesions by B-ultrasound							
Yes	62	39	16.8 ± 11.9	38	63	11	90
No	34	21	17.5 ± 11.8	16	39	5	50
χ^2	0.003		0.434	1.146		0.125	
<i>P</i> value	0.958		0.649	0.284		0.723	
Complicated with benign thyroidal diseases							
Yes	52	17	13.2 ± 8.6	14	55	0	69
No	50	49	20.3 ± 14.9	45	54	19	80
χ^2	10.533		12.407	11.301		14.931	
<i>P</i> value	0.001		0.001	0.001		0.000	
Tumor sites							
Unilateral	34	17	14.1 ± 12.0	13	38	1	50
Bilateral	68	49	18.6 ± 13.3	46	71	18	99
χ^2	1.085		4.130	2.980		6.381	
<i>P</i> value	0.297		0.044	0.084		0.012	
Number of tumors							
2 lesions	66	33	16.3 ± 12.1	26	73	8	91
≥ 3 lesions	36	33	18.7 ± 14.3	33	36	11	58
χ^2	3.581		1.281	8.298		2.505	
<i>P</i> value	0.058		0.259	0.004		0.113	

lateral neck lymph node dissection. Another 2 patients underwent repeated operation due to the recurrent contralateral remnant adenoma at postoperative 13 and 24 months (gland

lobe, isthmus and contralateral subtotal thyroidectomy, unilateral neck lymph dissection or VI area dissection). No patients undergoing radical resection died. The overall 1-, 2-, 5- and

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10-year survival rates achieved 98.2%, 97.4%, 96.5% and 96.5%. AJCC staging: 133 were evaluated as stage I, 7 stage II, 14 stage III, 11 stage IV and 3 stage IVc. AJCC staging was correlated with clinical prognosis ($\chi^2 = 168.832$, $P = 0.000$).

Discussion

Multifocal lesion is one of clinical characteristics of papillary thyroid carcinoma with an incidence of 18%-87% [3, 4]. In this study, the prevalence of multifocal lesions was 25.9%. In addition, the incidence of bilateral lesions was 69.6%. Multifocal lesions mainly occurred in male subjects with a family history of malignant thyroid tumors. However, the incidence of Goiter, Hashimoto's thyroiditis or alternative benign diseases in multifocal patients was lower compared with those in solitary lesions (41% vs 60%). These outcomes hinted that the pathogenesis of thyroid diseases probably varies. Multifocal lesions have a higher degree of malignant characteristics, manifested as a higher incidence of neck lymph metastasis and extra-thyroidal infiltration. In patients with multifocal lesions, male subjects with neck lymph nodular enlargement, bilateral tumor involvement and ≥ 3 lesions were more incline to a higher degree of malignancy. The papillary thyroid carcinoma subjects complicated with benign thyroid diseases presented with relatively small tumors and a relatively low incidence of lymph node metastasis. Most of them were primarily diagnosed with benign thyroid diseases, which further validate the results of small thyroid cancer investigations [5-7].

Thyroid cancer can be classified into two phenotypes: "dominant cancer" regarding cancer node as primary symptom and "sporadic cancer" manifested as benign diseases. The dominant cancer has a higher degree of malignancy. Whether multifocal lesions arise from thyroid gland metastasis or multiclonal origins remains controversial. Recent studies demonstrated that partial multifocal papillary thyroid carcinoma is of multiclonal origin [8]. In this clinical trial, the incidence of lymph nodular metastasis was relatively high in patients with non-small cancer, hinting that this event probably arises from thyroid gland metastasis. Nevertheless, Bansal et al [9] found that the percentage of papillary thyroid carcinoma patients with ≥ 3 lesions arising from multiclonal origin was high-

er, indicating that the number of lesions could not be used to identify its origin.

In this study, the proportion of multifocal papillary thyroid carcinoma subjects involving with bilateral thyroid was added up to 69.6%. Previous studies reported that patients presented with multifocal tumors after unilateral thyroidectomy and underwent total thyroidectomy within half a year. The incidence of contralateral small gland lobe cancer was 69.1%, significantly higher than 26.9% in patients with unilateral solitary lesions [10].

Consequently, it is necessary to perform total thyroidectomy in patients suffering from multifocal papillary thyroid carcinoma. However, only two cases (1.2%) had recurrent thyroid tumors in this study. For patients who did not undergo total thyroidectomy, it is equally a feasible option to excise remnant thyroid when they are suspected with recurrence. It has been recognized that neck lymph node dissection should be performed for patients with lymph node metastasis, whereas it remains debatable whether it should be conducted for those without lymph node metastasis detected by preoperative examination.

The British guidelines of thyroid cancer treatment suggested that multifocal cancer should be surgically treated with total thyroidectomy in combination with central lymph node dissection. Lateral lymph node dissection may be considered when palpable enlarged lymph nodes are detected in clinical settings [11-13]. American guidelines proposed that lymph node dissection should be performed for clinical cases with palpable lymph node enlargement [14]. The findings in this study and Park's investigation demonstrated that the incidence of lymph node metastasis in multifocal patients is higher compared with that in those with solitary lesions. In recent years, cNO patients without lymph node enlargement underwent conventional central dissection and the incidence of lymph node metastasis ranged from 47.6% to 51.3% [15-19]. We also conducted conventional central lymph node dissection in cNO patients and found the incidence of lymph node metastasis exceeded 30%. Among 6 patients with recurrent lymph node lesions, two cases did not undergo neck lymph node dissection and recurred in VI area at postoperative 10 and 14 months.

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Taken together, we recommend the application of conventional central neck lymph node dissection for papillary thyroid carcinoma patients. Lateral lymph node dissection may be considered when enlarged lymph nodes are detected in lateral area. Multifocal lesions possess a higher degree of biological malignancy compared with solitary cases. Total thyroidectomy combined with central lymph node dissection should be regarded as the standard surgery. AJCC grading remains a pivotal prognosis factor of multifocal papillary thyroid carcinoma.

Disclosure of conflict of interest

None.

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