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Original Article

Using foci number to predict central lymph node metastases of papillary thyroid microcarcinomas with multifocality

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Abstract: Objectives: The aim of our study is to analyze the clinicopathological characteristics and treatment options for papillary thyroid microcarcinomas with multifocality and investigated whether the number of foci in papillary thyroid microcarcinomas with multifocality can predict central lymph node metastases. Methods Records of 329 consecutive PTMC patients with multifocality, and who were treated surgically between 2003 and 2014 were reviewed. Patients with multifocality were identified by histopathology. The number of foci, size of the largest tumour, presence of extrathyroidal invasion, infiltration, and other clinicopathological parameters were collected and analyzed for all the cases. Results: Univariate analysis, age, sex, maximum tumour size, and extrathyroidal invasion were found to be significant prognostic factors (P = 0.001, 0.020, < 0.001, 0.043; respectively). Multivariate analysis found that age, sex, and maximum tumour size were independent prognostic factors for CLNM in PTMCs. Among them, Male patients (odds ratio 1.887; 95% confidence interval [CI] 1.053-3.380) and with maximum tumour size > 0.5 cm (odds ratio 2.819; 95% CI 1.721-4.616) were risk factors for increased incidence of CLNM. Patients ≥ 45 years (odds ratio 0. 497; 95% CI 0.309-0.800) were less likely to present with CLNM. However, extrathyroid invasion was not an independent predictor of CLNM according to our results. PTMCs with 2, 3, ≥ 4 foci had a significantly greater risk of CLNM (odds ratio 1.675, 2.360, 2.703; 95% CI 1.195-2.347, 1.425-3.906, 1.411-5.178; respectively) compared to PTMCs with unifocality. Conclusions: Foci numbers were linked to an increased incidence of central lymph node metastases in papillary thyroid microcarcinomas with multifocality, and we could choose to perform more radical treatment in patients with multifocality.

Keywords: Papillary thyroid carcinoma, lymph node, metastases, number of foci

Introduction

The World Health Organization defines a papillary thyroid microcarcinoma (PTMC) as a papillary thyroid carcinoma (PTC) with maximum diameter ≤ 10 mm. According to current literature, PTMC accounts for about 18.4 to 43.1% of all PTCs [1-3]. The widespread use of high-resolution ultrasonography and fine-needle aspiration biopsy (FNAB) over the last few decades has resulted in a dramatic increase in the rate of preoperative diagnosis of PTMC with multifocality [4]. However, the most important diagnostic measure for PTMC is the pathological examination of the thyroid specimen intra- or postoperatively. With the thinness of anatomical slices, the accuracy of pathological examination has increased, and pathological diagnosis of incidental PTMC with multisession is more frequent. However, the clinicopathological characteristics and resultant implications for the treatment of a subgroup of PTMC with multifocality are still debated. Further, it is unclear whether the number of foci in PTMC with multifocality predicts central lymph node metastases (CLNM). Therefore, we aim to analyze the clinicopathological characteristics and implications for the treatment of PTMC with multifocality and identify the risk factors for prognosis.

Methods

After approval by the institutional review board, the records of 329 consecutive PTMC patients with multifocality, and who were treated surgi-

Table 1. Clinical characteristics of patients with papillary thyroid microcarcinomas (PTMCs)

Characteristic	Total (n = 329)
Age(years)	
≤ 45	142 (43.2%)
> 45	187 (56.8%)
Sex	
Female	264 (80.2%)
Male	65 (19.8%)
Maximal tumor size (cm)	
≤ 0.5	154 (46.8%)
> 0.5	175 (53.2%)
Extrathyroidal invasion	
Present	85 (25.8%)
Absent	244 (74.2%)
Infiltration	
Present	13 (4.0%)
Absent	316 (96.0%)
Subtype	
Classic	309 (94.0%)
Follicular	20 (6.0%)
Multifocal PTMCs (n = 372)	
Unilateral	109 (33.1%)
Bilateral	220 (66.9%)
Hashimoto	
Present	98 (29.8%)
Absent	231 (70.2%)

CLNM: central lymph node metastasis.

cally at the Union hospital between 2003 and 2014, were reviewed. Patients with multifocality were identified by histopathology. The number of foci, size of the largest tumour, presence of extrathyroidal invasion, infiltration, and other clinicopathological parameters were recorded for all the cases.

Patients were classified into the following two groups: the PTMC with positive CLNM group and the negative lymph node metastasis group. Regardless of the disease stage or tumour size, we performed total thyroidectomy with bilateral central lymph neck dissection for cases where PTMC was diagnosed. Multifocality was defined as multiple malignancies in one lobe as well as bilaterally.

Statistical analysis

EpiData Software v3.1 (EpiData Association, Odense, Denmark) was used for primary clinical and histopathological data entry. Descriptive statistics were presented as summarized study data. Continuous variables were represented as mean ± standard deviation, while discrete variables were reported as a proportion and analyzed by the chi-square test or Fisher's exact test. Univariate analyses such as for age, sex, CLNM, and other clinicopathological parameters were performed by the Fisher's exact test or chi-square test, and multivariate analysis was carried out by binary logistic regression. All statistical analyses were performed using SPSS software (version 12.0, Chicago, IL, USA). All tests were two-sided and *P* values < 0.05 were considered statistically significant.

Results

Patient characteristics are shown in **Table 1**. The mean age at diagnosis was 47.08 ± 9.21 (range 14-75 years) years and the patients included 264 (80.2%) women and 65 (19.8%) men. The median tumour size was 0.60 ± 0.25 (range 0.05-1.0) cm. Tumour sizes were larger than 0.5 cm but less than 1.0 cm in 53.2% of the patients. CLNM were found in 121 (36.8%) patients. Extrathyroidal invasion and infiltration were present in 25.8% and 4.0% of patients respectively. Bilateral cancer of the thyroid was seen in 220 (66.9%) cases. Classic-type PTMC and Hashimoto's thyroiditis were observed in 94.0% and 29.8% of the cases respectively (**Table 1**). Total thyroidectomy and central lymph node dissection were performed in all cases.

In the univariate analysis, age, sex, maximum tumour size, and extrathyroidal invasion were found to be significant prognostic factors. However, the positive and negative CLNM groups were not significantly different for other parameters such as infiltration, subtype, bilateral, and presence of Hashimoto's thyroiditis (**Table 2**).

Multivariate analysis by binary logistic regression found that age, sex, and maximum tumour size were independent prognostic factors for CLNM in PTMCs. Among them, Male patients (odds ratio 1.887; 95% confidence interval [CI] 1.053-3.380) and with maximum tumour size > 0.5 cm (odds ratio 2.819; 95% CI 1.721-4.616) were risk factors for increased incidence of CLNM. Patients ≥ 45 years (odds ratio 0. 497;

Table 2. Univariate analysis of central lymph node metastases (CLNM) and clinicopathological characteristics in papillary thyroid microcarcinomas (PTMCs) with multifocality

Characteristic	CLNM positive N = 121	CLNM negative N = 208	P
Age (years)			
≤ 45	67	75	
> 45	54	133	= 0.001
Sex			
Female	89	175	
Male	32	33	= 0.020
Maximal tumor size (cm)			
≤ 0.5	36	118	
> 0.5	85	90	< 0.001
Extrathyroidal invasion			
Present	39	46	
Absent	82	162	= 0.043
Infiltration			
Present	6	7	
Absent	115	201	= 0.474
Subtype			
Classic	118	191	
Follicular	3	17	= 0.053
Location of foci			
Unilateral	37	72	
Bilateral	84	136	= 0.435
Hashimoto			
Present	38	60	
Absent	83	148	= 0.625

CLNM: central lymph node metastasis.

Table 3. Multivariate logistic regression analysis of central lymph node metastasis in papillary thyroid microcarcinomas with multifocality

	B	S.E.	Wald	Sig.	Exp (B)	95% C.I. for EXP (B)	
						Lower	Upper
Age	-.699	.243	8.272	0.004	0.497	0.309	0.800
Gender	.635	.297	4.555	0.033	1.887	1.053	3.380
Maximal tumor size	1.036	.252	16.956	0.000	2.819	1.721	4.616
Extrathyroidal invasion	.302	.274	1.217	0.270	1.353	.791	2.316

SE: standard error, CI: confidence interval, Sig.: significance.

Table 4. Association between multifocality and central lymph node metastases (CLNM) in papillary thyroid microcarcinomas

Characteristic	CLNM positive N = 266	CLNM negative N = 687	P
Multifocality			
Yes	121	208	< 0.001
No	145	479	

CLNM: central lymph node metastasis.

95% CI 0.309-0.800) were less likely to present with CLNM. However, extrathyroid invasion was not an independent predictor of CLNM according to our results (**Table 3**).

When data from 624 PTMCs with unifocality was compared to that from PTMCs with multifocality, we found a significant difference in the risk of CLNM between PTMCs with multifocality and those with unifocality (**Table 4**). Further, we compared the risk of CLNM to the number of foci. PTMCs with 2 foci had a significantly greater risk of CLNM (odds ratio 1.675; 95% CI 1.195-2.347) compared to PTMCs with unifocality. Subjects with 3 foci also had a significantly greater risk of CLNM (odds ratio, 2.360; 95% CI 1.425-3.906) compared to the group with unifocality. Similarly, patients in the group with ≥ 4 foci had significantly higher frequencies of CLNM (odds ratio 2.703; 95% CI 1.411-5.178) compared to the group with unifocality (**Table 5**).

Discussion

The increasing incidence of PTC, especially PTMC, may be

Table 5. Risk of central lymph node metastasis in papillary thyroid microcarcinomas according to the number of foci

	Number of multifocality			
	1	2	3	≥ 4
Lymph node metastasis				
NO. of patients (%)	145/624 (23.2%)	73/217 (33.6%)	30/72 (41.7%)	18/40 (45.0%)
OR (95% CI)	Reference	1.675 (1.195-2.347)	2.360 (1.425-3.906)	2.703 (1.411-5.178)
P-value		0.03	0.001	0.002

All ORs were adjusted for age (years) and sex. OR: odds ratio, CI: confidence interval.

due to the widespread use of imaging procedures like ultrasonography of the neck, which help to identify small thyroid nodules and incidental PTMCs [5]. On the other hand, the adoption of more aggressive surgical techniques such as total thyroidectomy plus central lymph node dissection also help to detect incidental PTMCs.

Although PTMC has been reported to have excellent prognosis according to many recent studies [6, 7], lymph node involvement, especially CLNM in PTMC, has been significantly associated with the presence of recurrent or persistent disease in many other studies [2, 8-11]. Therefore, it is natural to assume that more extensive surgery might reduce the risk of recurrence. However, which of the cases were more likely to exhibit lymph node metastasis, especially CLNM, and thus need more aggressive surgery was hotly debated. Moreover, few studies had demonstrated a relationship between clinicopathological characteristics and central lymph node involvement in PTMC with multifocality. So, it is important to identify the clinical and pathological features that contribute to aggressive cancers and CLNM [12, 13].

Multifocality often results from the development of multi-independent tumours with different clonal origins rather than intraglandular dissemination [14]. Multifocality within PTMC can cause more aggressive behaviour and is more likely to lead to CLNM and recurrence, which remains a troublesome problem [2, 8, 15-17]. Hay et al. reported that about 11% of multifocal tumours exhibited recurrence compared with 4% of unifocal tumours in PTMCs [8]. Therefore, a distinction between PTMCs with multifocality and unifocality is absolutely needed by physicians.

Multivariate analysis in our results demonstrated that age, sex, and maximum tumour size were independent risk factors for central lymph node involvement in PTMCs with multifocality. Our other results showed that multifocality increased the risk of CLNM compared to unifocal tumours. Further, subjects in the group who had more than 2 foci had a significantly greater risk of having CLNM compared to the group with unifocality (odds ratios 1.675, 2.360, and 2.703 respectively). Our results confirmed that the characteristics of multifocality in PTMCs were linked to the frequency of lymph node metastasis, which was suggested in many other studies [2, 9, 12, 18-21].

Although the national comprehensive cancer network guidelines recommend total thyroidectomy for PTCs where tumour size is more than 10 mm, and total thyroidectomy plus central lymph node dissection or lateral neck dissection for high-risk differentiated thyroid cancer, the treatment for PTMC is still not certain. Ito had supported an interesting idea that most PTMCs could be followed without any aggressive surgery immediately after diagnosis [22]. Moreover, some experts from other countries preferred unilateral lobectomy without radioactive remnant ablation for treatment of PTMCs [8, 23, 24]. On the other hand, some investigators suggested that total thyroidectomy and central lymph node dissection was an appropriate treatment for PTMCs when performed by experienced surgeons, which may result in lower local recurrence, allowing the pathologist to evaluate the whole thyroid and identify multifocality [9, 10, 18, 25, 26]. Our investigation had proved that multifocality was a risk factor for CLNM; therefore, we supported the idea that total thyroidectomy plus central lymph node dissection was a better treatment strategy for PTMCs with multifocality.

Some limitations, however, must be considered in our study. First, our study was a retrospective analysis. Lack of gene mutation information such as the BRAF mutation and prognostic information such disease-free survival or overall survival was not investigated [27]. In addition, the cases we included were from a single centre. Therefore, long-term follow-up, multicentre research, and prospective research are needed to describe the clinicopathological characteristics and resultant implications for treatment in PTMCs with multifocality.

Conclusion

To sum up, our results are useful in identifying PTMCs with multifocality, which are more likely to have CLNM and on the basis of this, we could choose to perform more radical treatment in patients with potentially aggressive tumours.

Disclosure of conflict of interest

None.

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