

Predicting factors of central lymph node metastases in patients with unilateral multifocal papillary thyroid microcarcinoma

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Background: Unilateral multifocal papillary thyroid microcarcinoma (UM-PTMC) is not rare, and the suitable extent of operation is controversial. Total thyroidectomy is associated with a high risk of hypoparathyroidism and recurrent laryngeal nerve injury. Hemithyroidectomy should be considered in patients without lymph node metastases. This study aimed to identify factors predicting central lymph node metastases (CLNM) in patients with UM-PTMC.

Methods: A total of 1,453 patients with thyroid cancer underwent surgery at our hospital from January 2018 to June 2018, and 115 patients with UM-PTMC were selected and assessed retrospectively. The relationship between CLNM and clinicopathologic features of UM-PTMC were analyzed by both univariate and multivariate analyses.

Results: Of the 115 patients with UM-PTMC, CLNM were confirmed by pathology in 57 patients. Univariate and multivariate analyses identified the sum diameter of all tumors (≥1.0 cm) [odds ratio (OR) =2.295; 95% confidence interval (CI): 1.036–5.086; P=0.041] and positive CLNM via ultrasonography (OR =5.882; 95% CI: 1.562–22.153; P=0.009) as independent predictors of CLNM.

Conclusions: CLNM are common in patients with UM-PTMC. The sum diameter of all tumors (\geq 1.0 cm) and positive CLNM via ultrasonography are independent risk factors for CLNM. Our data should be considered in the decision process relating to performing total thyroidectomy or hemithyroidectomy in patients with UM-PTMC.

Keywords: Central lymph node; metastases; multifocal; papillary thyroid microcarcinoma (PTMC); unilateral

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Introduction

Papillary thyroid carcinoma (PTC) is the most common histological subtype of thyroid cancer. Due to the increased use of diagnostic imaging and fine needle aspiration cytology, the proportion of newly diagnosed PTC has increased significantly in recent years. In China, the incidence of PTC increased more than 30% annually from 2000 to 2010 (1). This increase is mainly due to an increase in papillary thyroid microcarcinoma (PTMC), which is a type of PTC with a maximum tumor diameter of 10 mm (2-4).

The suitable extent of operation in patients with PTMC is still controversial, especially for unilateral multifocal papillary thyroid microcarcinoma (UM-PTMC). Some surgeons recommend total thyroidectomy (TT) because it is associated with a low risk of locoregional recurrence. But patients who accept TT would have an increased risk of hypoparathyroidism and recurrent laryngeal nerve

injury. Another disadvantage of TT is that high-dose lifelong thyroid hormone replacement would be required. Hemithyroidectomy (HT) is an alternative in patients with UM-PTMC, especially for those without lymph node metastases (LNM). The most common site of LNM, the central compartment, has a metastasis frequency of 16.9–35.0% in PTMC (1,5). Therefore, it is important to identify the predictors of central lymph node metastases (CLNM) in patients with UM-PTMC. This is important for determining the most appropriate surgical approach, for both patients and surgeons. HT is appropriate for UM-PTMC without CLNM. The aim of the present study was to identify the predictors of CLNM in patients with UM-PTMC.

Methods

Study design and participants

A total of 1,453 patients with thyroid cancer underwent surgery at our hospital from January 2018 to June 2018. All the medical records were retrospectively reviewed by two independent doctors. Patients were selected on the basis of the following inclusion criteria: (I) unilateral nodules revealed by preoperative ultrasonography, (II) UM-PTMC diagnosed by postoperative pathology, (III) TT or HT plus central lymph node dissection was performed, and (IV) the medical records of patients were complete. Patients who had previous radiation exposure, thyroid operation history, and coexisting head and neck tumors were excluded. A retrospective database was constructed. Demographic characteristics, thyroid function, ultrasonography outcomes, operation details, and pathological results were reviewed and analyzed. A tumor was defined as multifocal if at least 2 foci were found. The largest lesion was designated as the main focus. The study was approved by the Institutional Review Board of Peking Union Medical College Hospital (S-K1057). The requirement of informed consent for publication of data was waived owing to the retrospective nature of the study.

Treatment

All patients underwent routine thyroid function test and ultrasonography before operation. Ultrasonography was performed by specially trained sonographers with more than 5 years of experience in thyroid imaging. Prior to surgery, both the benefits and risks of TT and HT were explained by surgeons, and the surgical approach was decided according to the patients' willingness. All patients underwent operation under general anesthesia in the supine position with hypsokinesis of the head. Regardless of whether TT or HT was performed, all patients underwent central compartment lymph node dissection. Lateral neck lymph node dissection was performed only in case where metastases were revealed by preoperative ultrasonography.

Postoperative pathological diagnosis was confirmed by two different pathologists with at least 5 years of experience in thyroid pathology. All patients were postoperatively administered oral euthyrox for suppressive therapy. Thyroid stimulating hormone level was maintained at approximately 0.1 µIU/mL. All patients were followed up for at least 1 year postoperatively and underwent ultrasonography every 6 months to exclude tumor residual and recurrence. For patients who underwent HT, the contralateral lobe was examined extremely carefully to exclude any nodules.

Statistical analysis

The Statistical Package for Social Sciences software (SPSS, version 25.0, IBM Corp., Armonk, NY, USA) was used to perform statistical analysis. Linear variables were presented as mean \pm standard deviation. Categorical variables were described by absolute number or frequency. Differences between study groups were analyzed by the χ^2 test or Student's *t*-test as appropriate. Logistic multivariate regression analyses were performed to identify independent predicting factors for CLNM in patients with UM-PTMC. A P value <0.05 was considered statistically significant.

Results

A total of 115 patients with UM-PTMC who underwent surgery from January 2018 to June 2018 were selected (*Figure 1*). The mean age was 42.2±10.8 years (range, 19– 72 years). Thirty-four (29.6%) of the patients were males. One hundred and one (87.8%) patients were asymptomatic and incidentally diagnosed with thyroid node. Only 14 (12.2%) patients had symptoms such as hoarseness, dysphagia, and cough. On follow-up, no residual tumor or tumor recurrence was found on ultrasonography performed every 6 months after the operation. For patients who underwent HT, preoperative ultrasonography revealed no contralateral nodule, and the result was confirmed by other ultrasonography every 6 months after surgery.

Based on postoperative pathology, patients were divided

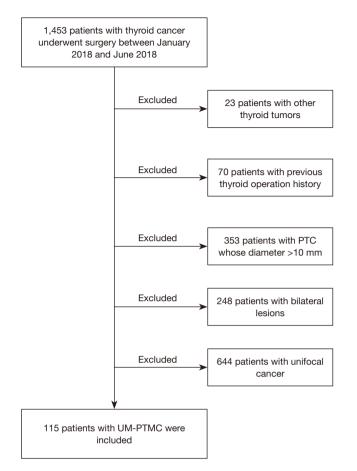


Figure 1 Flow diagram of inclusion criteria of study participants. PTC, papillary thyroid carcinoma; UM-PTMC, unilateral multifocal papillary thyroid microcarcinoma.

into two groups: CLNM positive (n=57, 49.6%) and CLNM negative (n=58, 50.4%). The demographic data and outcomes of thyroid function were analyzed and compared between the two groups (Table 1), and no significant difference was found. Tumors were located in the left lobe in 58 patients and in the right lobe in 57 patients. Mean tumor diameter of the main focus was 0.6±0.2 cm (range, 0.1–1.0 cm), and mean sum diameter of all foci was $0.9\pm$ 0.4 cm (range, 0.2-2.1 cm). TT and HT were performed in 69 (60.0%) and 46 (40.0%) patients, respectively. The outcomes of ultrasonography, scope of surgery, and pathological results were compared between the two groups (Table 2). In comparing the CLNM positive and CLNM negative groups, statistically significant differences were found for sum diameter of all foci, extrathyroidal invasion, lateral neck LNM, larger foci number (\geq 3), and positive CLNM via ultrasonography.

Multivariate logistic regression analyses were performed to examine associations between select variables and CLNM. Two variables proved to be independently associated with CLNM. They were larger sum diameter of all foci (\geq 1.0 cm) and positive CLNM via ultrasonography, with odds ratios of 2.295 and 5.882, respectively (*Table 3*).

Discussion

The present study showed that 87.8% of patients with UM-PTMC were asymptomatic, and the rate of CLNM in UM-PTMC was 49.6%. A larger sum diameter of all foci (≥

Table 1 Demographic data and thyroid functions of patients with UM-PTMC

Variables	Total (n=115)	CLNM (+) (n=57)	CLNM (-) (n=58)	P value
Male/female (n)	34/81	20/37	14/44	0.198
Age (years)	42.2±10.8	41.1±11.3	43.3±10.2	0.273
BMI (kg/m²)	24.7±3.3	25.0±3.5	24.4±3.1	0.315
Thyroid cancer family history (n)	3	1	2	1.000
Smoking (n)	7	3	4	1.000
FT3 (pg/mL)	3.1±0.5	3.1±0.5	3.1±0.5	0.280
FT4 (ng/dL)	1.3±0.5	1.2±0.1	1.3±0.7	0.565
TSH (μIU/mL)	2.1±1.5	2.0±1.2	2.2±1.7	0.437
Hashimoto's thyroiditis (n)	30	11	19	0.100

UM-PTMC, unilateral multifocal papillary thyroid microcarcinoma; CLNM, central lymph node metastases; BMI, body mass index; FT3, free triiodothyronine; FT4, free thyroxine; TSH, thyroid stimulating hormone.

Variables	Total (n=115)	CLNM (+) (n=57)	CLNM (–) (n=58)	P value		
Tumor location (LL/RL) (n)	58/57	28/29	30/28	0.780		
TT/HT (n)	69/46	37/20	32/26	0.286		
Diameter of the main focus (cm)	0.6±0.2	0.6±0.2	0.5±0.2	0.100		
Sum diameter of all foci (cm)	0.9±0.3	1.0±0.4	0.8±0.3	0.012		
Foci number ≥3 (n)	24	17	7	0.019		
Capsular invasion (n)	75	40	35	0.268		
Extrathyroidal invasion (n)	13	10	3	0.036		
Ki67 ≥3% (n)	21	10	11	0.844		
CLNM via ultrasonography (n)	17	14	3	0.003		
Lateral neck metastases (n)	12	10	2	0.013		

Table 2 Detailed data regarding operation, ultrasonography, and pathology for patients with UM-PTMC

UM-PTMC, unilateral multifocal papillary thyroid microcarcinoma; CLNM, central lymph node metastases; LL, left lobe; RL, right lobe; TT, total thyroidectomy; HT, hemithyroidectomy.

Table 3 Multivariate analyses for predicting factors of CLNM in patients with UM-PTMC

Variables	P value	OR	95% CI
Sum diameter of all tumors (≥1.0 cm)	0.041	2.295	1.036–5.086
Positive CLNM via ultrasonography	0.009	5.882	1.562-22.153
Tumor number (≥3)	0.114	-	-
Extrathyroidal invasion	0.132	-	-
Lateral neck lymph node metastases	0.322	_	-

CLNM, central lymph node metastases; UM-PTMC, unilateral multifocal papillary thyroid microcarcinoma; OR, odds ratio; 95% CI, 95% confidence interval.

1.0 cm) and positive CLNM via ultrasonography were found to be independently associated with CLNM. As such, we recommend that patients with UM-PTMC who exhibit these two risk factors undergo TT during their initial surgery.

Advancement in ultrasound technology and increased uptake of health examination have resulted in an increase in the diagnosis of PTMC. It was reported that more than 60% of all thyroid cancers are PTMC (6). Micro tumor means early tumor staging and good prognosis. Conversely, multifocal tumor is associated with more frequent LNM and an increased risk of recurrence (1,7,8). However, an investigation of 2,309 patients by Kim *et al.* revealed that multifocality was not an independent risk factor for tumor recurrence and persistence in patients with PTMC (9). Therefore, the suitable treatment for UM-PTMC remains controversial, and TT may not be the only option for patients with UM-PTMC. To avoid recurrent laryngeal nerve injury and hypoparathyroidism, HT should be considered in UM-PTMC without LNM. Thus, it is important to determine whether LNM are present before surgical intervention. The preferred method for thyroid examination and detecting the absence of LNM is preoperative ultrasonography, which is affordable and noninvasive. Metastatic lymph nodes often manifest as round shape, cystic change, microcalcification, hypoechogenicity, and hypervascularity (10). Ultrasonography might not detect micro or deep lymph nodes. The sensitivity of preoperative ultrasonography is not high enough and is reported as 13–30% (6,11,12). A new assessment method for predicting CLNM in patients with UM-PTMC needs to be proposed to assist in determining surgical pattern.

Previous studies have identified risk factors for CLNM in patients with PTMC (13-16). However, very few of

these studies focused on the predictors of UM-PTMC. The present study clarifies the association between several variables and CLNM in patients with UM-PTMC. Of those variables, larger sum diameter of all foci (≥1.0 cm) and positive CLNM via ultrasonography are proved to be independent risk factors. Larger tumor size contributes to the tumors being more aggressive and is an important factor in tumor staging system. LNM are more frequently found in PTMC with larger tumor size (17-20). Multifocality may arise from multiple independent origins or from intraglandular spread of a single main focus (21-23). Lu et al. used next-generation sequencing technologies and found that 75% of multicentric PTC cases arose as independent tumors (23). Though it is not included in the tumor staging system, multifocality has been reported as a predictor of CLNM in patients with PTMC (1,7,18,24). UM-PTMC with larger sum diameter of all foci (≥ 1.0 cm) contains both variables. This could explain why a larger sum diameter of all foci is an independent predictor. Zhao et al. studied 212 patients with PTMC and recommended routine central lymph node dissection in patients with multifocal PTMC with total tumor diameter >1 cm (25). Liu et al. reported on 1,102 patients with PTC and suggested that total tumor diameter is a relatively more accurate criterion for tumor size of PTC (2). Feng et al. reported 442 patients with PTC and found that multifocal PTMC with a total tumor diameter >1 cm was more aggressive than unifocal PTMC or multifocal PTMC with total tumor diameter ≤ 1 cm (26). Our result was consistent with the results of the abovementioned studies. Though the sensitivity of preoperative ultrasonography in detecting CLNM is low (24.6%, 14/57), its specificity is high (82.4%, 14/17) (Table 2). Similar to our study, a specificity of 88.4-95.2% has been reported by previous studies (12,27). This may be the reason why positive CLNM via ultrasonography could be a potential risk factor.

Between the CLNM positive and negative groups, several variables show significant differences during univariate analysis but are not significant in multivariate analysis. These include tumor number (\geq 3), extrathyroidal invasion, and lateral neck LNM. Some previous studies also reported that young age (<45 years), male gender, and lymphovascular invasion could be the predictors of LNM (1,24,28). In the present study, no significant association was found between the abovementioned variables and CLNM. A possible explanation could be that UM-PTMC has characteristics that differ from those of other thyroid cancers and that the sample size was small.

At present, prophylactic lymph node dissection is recommended in patients with multifocal thyroid cancer (10,29). Xue et al. suggested TT in UT-PTMC because it had a lower recurrence rate than that of HT (30). However, it was reported that multifocality was not an independent predictor of CLNM (20) and had no association with mortality (31). Choi et al. retrospectively reviewed 2,390 patients with PTC and found that the prognostic value of multifocality was more significant in PTC of >1 cm tumor size than in PTMC (32). Thus, the best approach to manage patients with UT-PTMC remains controversial. The debate centers on whether it is necessary to remove the contralateral lobe which would lead to more complications, such as nerve damage and hypoparathyroidism, while conservative treatment would lead to an increased recurrence rate. Based on our findings, larger sum diameter of all foci (≥ 1.0 cm) and positive CLNM via ultrasonography are independent risk factors of CLNM in patients with UM-PTMC, and we recommend TT in UM-PTMC patients with these two variables.

There are some limitations of this study. First, because of its retrospective nature, the patient volume, registration information, and inspection items could not be designed beforehand. Second, some patients underwent HT and the unilateral feature was confirmed by ultrasonography. Subclinical contralateral microcarcinoma might exist and result in wrong grouping. Third, the duration of follow-up was short. To overcome these limitations and provide more reliable data, prospective, randomized, controlled, and multicenter clinical trials are necessary.

In conclusion, our results suggest that the sum diameter of all tumors (\geq 1.0 cm) and positive CLNM via ultrasonography are independent factors for CLNM in patients with UM-PTMC. Therefore, these factors should be considered by surgeons when deciding whether to perform TT in patients with UM-PTMC.

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Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.

Wu et al. Predicting factors of CLNM in UM-PTMC

org/10.21037/gs.2020.03.27). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was approved by the Institutional Review Board of Peking Union Medical College Hospital (S-K1057). The requirement of informed consent for publication of data was waived owing to the retrospective nature of the study.

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Gland Surgery, Vol 9, No 3 June 2020

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