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ORIGINAL ARTICLE

Total tumor diameter: the neglected value in papillary thyroid microcarcinoma

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Abstract

Background Tumor multifocality is not uncommon in papillary thyroid carcinoma (PTC), especially in micro-PTC. However, assessing the size of the largest tumor may underestimate effect of additional foci. We aimed to investigate the effect of total tumor diameter (TTD) on clinicopathological features of micro-PTC.

Methods Data from 442 patients who underwent thyroidectomy with cervical lymph node dissection for PTC were retrospectively analyzed. Patients were classified into subgroups according to multifocality and TTD. The relationships of clinicopathological features among these groups were analyzed.

Results Multifocality was observed in 119 patients (26.9%). TTD > 1 cm and presence of extrathyroidal extension (ETE) were significantly higher in multifocal tumors compared to unifocal tumor ($P < 0.001$, $P = 0.016$, respectively). When comparing multifocal micro-PTC with TTD > 1 cm to those with unifocal micro-PTC or multifocal micro-PTC with TTD ≤ 1 cm, the proportions of cases with ETE, central lymph node metastasis (CLNM), and lateral lymph node metastasis (LLNM) were significantly higher (all $P < 0.05$). There was no significant difference in terms of these parameters between multifocal micro-PTC with TTD > 1 cm and macro-PTC or multifocal macro-PTC. The risk of CLNM was 2.056 ($P = 0.044$) times higher in multifocal micro-PTC with TTD > 1 cm than in unifocal micro-PTC.

Conclusion For multifocal micro-PTC, TTD can better assess the aggressiveness of the tumor. Multifocal micro-PTC with TTD > 1 cm was more aggressive than unifocal micro-PTC or multifocal micro-PTC with TTD ≤ 1 cm.

Keywords Papillary thyroid carcinoma · Multifocality · Total tumor diameter · Lymph node metastases · Recurrence-free survival

Introduction

Over the past few decades, the incidence of thyroid cancer (TC), especially papillary thyroid cancer (PTC), is rising at the fastest rate of all malignancies [1, 2]. PTC is generally considered as an indolent disease, but some PTCs with certain clinicopathological characteristics show the aggressiveness, resulting in poor prognosis [3]. Multifocal PTC, which developed from multiple independent primary tumors or resulted from the intraglandular dissemination of primary tumor, had the prevalence ranged between 20.0 and 36.1% [4–6].

Multifocal PTC was reported to associate with poor disease-specific survival [6–8] and aggressive features [5, 7, 9, 10]. However, the American Thyroid Association (ATA) guidelines and the European Thyroid Association (ETA) guidelines did not consider the multifocality as a worse prognostic factor for microcarcinoma (diameter ≤ 1 cm) [11, 12], and the treatment strategies for multifocal microcarcinomas were similar with unifocal microcarcinomas.

Unlike the primary focus, most additional tumor lesions were too small to be diagnosed preoperatively in multifocal PTC [4]. The American Joint Committee on Cancer (AJCC) tumor-node-metastasis (TNM) classification system [13], along with the ATA guidelines [11], defined the tumor size according to the biggest tumor independent of tumor number in multifocal tumors. The influence of additional tumors of multifocal PTC on aggressive behavior remains unclear.

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So far, despite few studies suggesting that multifocal papillary thyroid microcarcinoma with total tumor diameter (TTD) > 1 cm had more aggressive clinicopathologic features than unifocal papillary thyroid microcarcinoma, the importance of TTD in multifocal PTC is still overlooked [14, 15]. In this study, we aimed to investigate whether patients with multifocal microcarcinomas with TTD > 1 cm share the same clinicopathological features and recurrence-free survival (RFS) as those with traditional microcarcinomas. In addition, we compared the clinicopathologic features and RFS of patients subdivided by multifocality and TTD.

Materials and methods

Patients

This retrospective study was approved by the Institutional Review Board of Changzhou First People's Hospital. All participants gave written informed consent for their clinical records to be used in this study. A total of 487 consecutive patients with pathologically proven TC who underwent thyroidectomy from January 2011 to January 2018 at the Changzhou First People's Hospital were retrospectively reviewed from our department prospective surgical database. Patients were excluded from the study if they have any of the following factors: (1) had another malignancy before thyroidectomy; (2) reoperation; (3) non-PTCs (medullary/follicular/anaplastic) or mixed-type PTC; (4) distant metastasis at diagnosis; (5) had upper mediastinal node metastasis detected before thyroidectomy; (6) underwent non-curative surgery. In total, 442 patients were finally included and evaluated.

Surgical procedures

All patients underwent ultrasonography (US), computed tomography (CT) or ^{18}F-FDG PET to evaluate their primary lesions and LNM. US of the neck was routinely used. With the discovery of thyroid nodule(s), a complete examination focusing on the thyroid gland and adjacent cervical lymph nodes would be carried out. For example, more detailed US by experienced doctors, or CT, 18F-FDG PET to find out the other neglected nodules and to evaluate suspicious nodules were all recommended. Moreover, serum thyroid-stimulating hormone (TSH) would be measured. If the serum TSH was subnormal, a radionuclide thyroid scan (^{123}I) would be used to assess the nodules and to find out the other neglected nodules. A fine-needle aspiration (FNA) was performed for thyroid nodules > 1 cm in diameter with malignant signs by US. Thyroid nodules with a diameter of ≤ 1 cm had one of the following conditions, which may be considered for FNA: (1) US examination indicated a malignant sign of the nodule; (2) with abnormal US imaging of cervical lymph nodes; (3) with a history of cervical radiation exposure or exposure to radiation pollution; (4) with a history of familial thyroid carcinoma; (5) ^{18}F-FDG PET imaging was positive; (6) accompanied by abnormal increase in serum calcitonin levels. For clinically positive lateral lymph node metastasis (LLNM) or intraoperative suspected LLNM, total thyroidectomy (TT) with central neck dissection (CND) and therapeutic ipsilateral lateral neck dissection (LND) would be performed. LND was not performed in cN0 PTC patients (absence of any pre- or intra-operative evidence of lymph node disease), while prophylactic CND was performed in all cN0 PTC patients. Based on FNA or other imaging diagnosis, patients with preoperatively proven or suspected unilateral malignant thyroid nodule would undergo unilateral thyroid lobectomy, and patients with preoperatively proven or suspected bilateral malignant thyroid nodules would undergo TT. LND was performed in the usual fashion from at least level II to level V, sparing the internal jugular vein, spinal accessory nerve, and sternocleidomastoid muscle [16]. CND included prelaryngeal, pretracheal and both the right and left paratracheal nodal basins [17]. All lymph node specimens were separated by the surgeon according to neck levels, and were sent to the department of pathology for paraffin fixation and histological analysis.

Definition

Two or more experienced pathologists microscopically reviewed and cross-checked all pathology specimens. Multifocality was defined as two or more PTC lesions within the thyroid. Micro-PTC was defined as PTC ≤ 1 cm in its maximum diameter while macro-PTC was PTC > 1 cm in its maximum diameter. The sum of the maximal diameter of each tumor foci was used to calculate TTD. Gross extrathyroidal extension (ETE) was defined as the tumor involving strap muscles (sternohyoid, sternothyroid, thyrohyoid or omohyoid muscles), or extending to surrounding structures such as larynx, trachea, esophagus, recurrent laryngeal nerve, subcutaneous soft tissue, skin, internal jugular vein, or carotid artery. Minimal ETE was defined as the primary tumor extending through the thyroid capsule to perithyroidal soft tissue: perithyroidal fat. Based on multifocality and TTD, patients were subdivided into the following groups: unifocal micro-PTC, multifocal micro-PTC with TTD ≤ 1 cm, multifocal micro-PTC with TTD > 1 cm, unifocal macro-PTC, and multifocal macro-PTC. TNM staging was based on the AJCC, 8th edition [13]. The criteria for remission was defined as: (1) no evidence of tumor recurrence in clinical or radiologic examination, and (2) serum thyroglobulin (Tg) levels of < 2 ng/mL during TSH stimulation and < 1 ng/mL during TSH suppression in the absence of anti-Tg antibodies [18–20]. Patients with persistent disease

were those who never met remission criteria throughout the follow-up periods. Disease recurrence, which included the local, regional, and distant recurrence, was defined as new evidence of pathologically proven recurrence in patients who initially met the criteria of remission. After the radiographic or biochemical examinations, histological examination of new lesion would be performed to verify whether the lesion was the recurrent PTC. Physical examinations, US of the neck chest radiography, whole-body iodine scanning, and serum thyroid function (free thyroxin, TSH, and Tg) were used for all patients every 6 months for 2 years, and annually thereafter. Further imaging examinations or histological confirmation were used when the level of Tg and/or Tg antibodies significantly elevated.

Postoperative management and follow-up

Postoperative suppressive levothyroxine (LT4) treatment was administered to all patients. TSH suppression therapy (serum TSH level below 0.5 mIU/L) with LT4 with or without radioactive iodine (RAI) ablation was used for patients underwent total thyroidectomy. The criteria for RAI ablation in our institution were patients with age > 45 years old with tumor size > 4 cm, patients of any age with gross ETE (T4 disease), or any patient with distant metastasis. When patients had an intermediate-to-high risk for recurrence, such as primary tumors ranging from 1 to 4 cm confined to the thyroid, high-risk histological subtypes (tall cell, columnar and solid variants of PTC), vascular invasion, or cervical LNM, the choice to receive RAI ablation was determined by patients after discussion with surgeon about other individualized risk factors, such as follow-up compliance, gender and family history. Follow-up data were obtained by outpatient consultations.

Statistical analyses

All statistical analyses were carried out using the SPSS v 25.0 software (Chicago, IL, USA). The continuous variables were expressed as the means ± standard deviations (SD). The χ^2 test or Fisher's exact test was used, as appropriate, for categorical data, whereas continuous variables were compared with Student's *t* tests or the Mann–Whitney *U* test. Univariate analyses for the comparison between patient groups were performed using Pearson's Chi-square test or Fisher's exact test. Binary logistic regression test was used for multivariate analysis of statistically significant variables from the univariate analysis. The Cox proportional hazards model was used to analyze the potential relationship between clinicopathological variables and RFS. Multivariate Cox proportional hazard regression analyses were performed with backward elimination from variables with *P* values < 0.05 on univariate analyses. The hazard ratio (HR) and confidence intervals (CI) were calculated. RFS curves were calculated using the Kaplan–Meier method, and the log-rank test was used to evaluate the differences between curves. $P < 0.05$ was considered to have statistical significance.

Results

Baseline clinicopathological characteristics of PTC patients

The key clinicopathological characteristics are summarized in Table 1. Our study included 109 men (24.7%) and 333 women (75.3%), with a mean ± SD age of 45.4 ± 12.3 years. The mean ± SD diameter of the primary thyroid tumor was 1.23 ± 0.93 cm, 194 (43.9%) of which were larger than 1 cm. Unifocal lesion was found in 323 patients (73.1%) and multifocal lesions were found in 119 patients (26.9%). Among the multifocal PTC, 91 (20.6%) had 2 foci, 20 (4.5%) had 3 foci and 8 (1.8%) had 4 foci. The minimal ETE, gross ETE and vascular invasion were observed in 51 (11.5%), 16 (3.6%) and 25 (5.7%) patients, respectively. Sixty-one patients were detected the LLNM preoperatively while 19 patients were suspected of LLNM during surgery, and LND was performed in these patients (18.1%). The remaining 362 patients (81.9%) underwent CND only. The postoperative examination confirmed that: 209 patients (47.3%) had nodes removed without metastases, 168 patients (38.0%) had central lymph node metastasis (CLNM) only, 55 patients (12.4%) had both CLNM and LLNM, and 10 patients (2.1%) had the skip metastases (LLNM without CLNM). TNM stage was I in 348 (78.7%), II in 89 (20.1%), and III in 5 (1.1%) patients. Of 64 PTC patients who were performed BRAF mutation analysis, 56 (87.5%) had BRAF mutation positivity.

Postoperative follow-up ranged from 11 to 99 months (average follow-up period: 43 months). During follow-up, 50 patients (11.3%) developed recurrent disease, including 31 patients (7.0%) had cervical lymph nodes recurrence, 12 patients (2.7%) had thyroid bed recurrence and 7 patients (1.6%) had lung recurrence.

Comparison of unifocal and multifocal tumors

Table 2 shows the results of relationships among clinicopathological variables and multifocality. In the univariate analysis, TTD > 1 cm and the presence of ETE (minimal and gross ETE) were significant higher in multifocal tumors than in unifocal tumors ($P < 0.001$, $P = 0.016$, respectively). According to the multivariate analysis, TTD > 1 cm (adjusted OR 6.654, $P < 0.001$) was the only significant independent factor for a high risk of multifocal tumors.

Table 1 Baseline clinicopathological characteristics of 442 PTC patients

Clinicopathological characteristics	No. (%)
Sex	
Male	109 (24.7%)
Female	333 (75.3%)
Age (year)	
Mean ± SD	45.4 ± 12.3
≥ 45	219 (49.5%)
< 45	223 (50.5%)
Primary tumor diameter (cm)	
Mean ± SD (range)	1.23 ± 0.93 (0.10–6.00)
≤ 1	248 (56.1%)
> 1	194 (43.9%)
TTD (cm)	
Mean ± SD	1.69 ± 0.97
≤ 1	201 (45.5%)
> 1	241 (54.5%)
The number of foci	
1	323 (73.1%)
2	91 (20.6%)
3	20 (4.5%)
4	8 (1.8%)
Multifocality	
Presence	119 (26.9%)
Absence	323 (73.1%)
BRAF mutation[a]	
Presence	56 (87.5%)
Absence	8 (12.5%)
ETE	
Presence	67 (15.2%)
Absence	375 (84.8%)
ETE	
Minimal ETE	51 (11.5%)
Gross ETE	16 (3.6%)
Absence	375 (84.8%)
Vascular invasion	
Presence	25 (5.7%)
Absence	417 (94.3%)
Neck dissection	
CND	362 (81.9%)
CND + LND	80 (18.1%)
LNM	
CLNM only	168 (38.0%)
LLNM only	10 (2.1%)
CLNM and LLNM	55 (12.4%)
Absence	209 (47.3%)
AJCC TNM staging	
Stage I	348 (78.7%)
Stage II	89 (20.1%)
Stage III	5 (1.1%)
Recurrence	50 (11.3%)
LNs	31 (7.0%)
Thyroid bed	12 (2.7%)
Lung	7 (1.6%)

PTC papillary thyroid carcinoma, *SD* standard deviation, *TTD* total tumor diameter, *ETE* extrathyroidal extension, *CND* central neck dissection, *LND* lateral neck dissection, *CLNM* central lymph node metastasis, *LLNM* lateral lymph node metastasis, *LN* lymph node, *AJCC* American Joint Committee on Cancer

[a]BRAF mutation analysis was started in 2017 and it was performed in 64 patients with PTC

Clinicopathological characteristics according to multifocality and TTD

For multifocal PTC patients, we used the TTD of each specimen as a new parameter in further analysis. The distribution of patients was as follows: 182 (41.2%) patients in unifocal micro-PTC, 19 (4.3%) in multifocal micro-PTC with TTD ≤ 1 cm, 47 (10.6%) in multifocal micro-PTC with TTD > 1 cm, 141 (31.9%) in unifocal macro-PTC, and 53 (12.0%) in multifocal macro-PTC (Table 3).

Clinicopathologic features of multifocal micro-PTC with TTD > 1 cm were compared with unifocal micro-PTC. Proportions of ETE, CLNM, and LLNM were higher in multifocal micro-PTC with TTD > 1 cm ($P = 0.006$, $P = 0.021$ and $P = 0.039$, respectively). Similarly, proportions of ETE, CLNM, and LLNM were significantly higher in multifocal micro-PTC with TTD > 1 cm than in multifocal micro-PTC with TTD ≤ 1 cm ($P = 0.023$, $P = 0.033$ and $P = 0.024$, respectively). Other clinicopathologic features, including BRAF mutation, vascular invasion, were not observed any significant differences.

Clinicopathologic features of multifocal micro-PTC with TTD > 1 cm were also compared with unifocal macro-PTC or with multifocal macro-PTC. There were no significant differences in terms of these clinicopathologic features between these groups.

Predictors of CLNM

Association between clinicopathological characteristics and CLNM is shown in Table 4. In the univariate analysis, clinicopathologic features, such as sex, age, primary tumor diameter, the number of foci, ETE, vascular invasion and LLNM were significantly associated with CLNM (all $P < 0.050$). Moreover, ratios of multifocal micro-PTC with TTD > 1 cm, unifocal macro-PTC and multifocal macro-PTC were higher in patients with CLNM than in patients without CLNM (11.7% vs. 9.6%, 40.4% vs. 23.3%, 15.7% vs. 8.2%, $P < 0.001$).

Table 2 Clinicopathologic characteristics of patients with unifocal and multifocal PTC

Clinicopathological characteristics	Univariate analysis		*P* value	Multivariate analysis	
	Unifocal $n=323$ (73.1%)	Multifocal $n=119$ (26.9%)		Adjusted OR (95% CI)	*P* value
Sex					
Male	79 (24.5%)	30 (25.2%)			
Female	244 (75.5%)	89 (74.8%)	0.871		
Age (year)					
≥45	161 (49.8%)	58 (48.7%)			
<45	162 (50.2%)	61 (51.3%)	0.837		
Primary tumor diameter (cm)					
Mean ± SD	1.22 ± 0.95	1.27 ± 0.87	0.566		
≤1	182 (56.3%)	66 (55.5%)			
>1	141 (43.7%)	53 (44.5%)	0.868		
TTD (cm)					
≤1	182 (56.3%)	19 (16.0%)		1	
>1	141 (43.7%)	100 (84.0%)	**<0.001**	6.654 (3.876–11.425)	**<0.001**
BRAF mutation[a]					
Absence	6 (13.6%)	2 (10.0%)			
Presence	38 (86.4%)	18 (90.0%)	1.000		
ETE					
Absence	284 (87.9%)	91 (76.5%)		1	
Minimal ETE	30 (9.3%)	21 (17.6%)		1.665 (0.442–6.267)	0.451
Gross ETE	9 (2.8%)	7 (5.9%)	**0.016**	2.525 (0.725–8.791)	0.146
Vascular invasion					
Absence	305 (94.4%)	112 (94.1%)			
Presence	18 (5.6%)	7 (5.9%)	0.901		
CLNM					
Absence	166 (51.4%)	59 (44.5%)			
Presence	157 (48.6%)	60 (55.5%)	0.201		
LLNM					
Absence	280 (86.7%)	97 (81.5%)			
Presence	43 (13.3%)	22 (18.5%)	0.173		
AJCC TNM staging					
Stage I	257 (79.6%)	91 (76.5%)			
Stage II	63 (19.5%)	26 (21.8%)			
Stage III	3 (0.9%)	2 (1.7%)	0.691		

Bold values indicate $P<0.05$

PTC papillary thyroid carcinoma, *SD* standard deviation, *TTD* total tumor diameter, *ETE* extrathyroidal extension, *CLNM* central lymph node metastasis, *LLNM* lateral lymph node metastasis, *AJCC* American Joint Committee on Cancer

[a]BRAF mutation analysis was started in 2017 and it was performed in 64 patients with PTC

In the multivariate analysis, when patients with unifocal micro-PTC were taken as reference, CLNM risk was 2.056 times ($P=0.044$) higher in multifocal micro-PTC with TTD >1 cm, 2.436 times ($P<0.001$) higher in unifocal macro-PTC, and 2.430 times ($P<0.001$) higher in multifocal macro-PTC. Primary tumor diameter > 1 cm, presence of ETE and LLNM were also independent predictive factors for LLNM (all $P<0.050$).

Predictors of LLNM

Table 5 shows the association between LLNM and clinicopathological characteristics. Ratios of multifocal micro-PTC with TTD > 1 cm, unifocal macro-PTC and multifocal macro-PTC were higher in patients with LLNM than in patients without LLNM (10.8% vs. 10.6%, 52.3% vs. 28.4%, 23.1% vs. 10.1%, $P<0.001$). Primary tumor diameter

Table 3 Comparison of histopathological features between multifocal micro-PTC with TTD >1 cm and other tumor groups

Variables	Micro-PTC			Macro-PTC		*P* value	Multifocal micro-PTC with TTD > 1 cm			
	Unifocal	Multifocal with TTD ≤ 1 cm	Multifocal with TTD > 1 cm	Unifocal	Multifocal		Unifocal micro-PTC	Multifocal micro-PTC with TTD ≤ 1 cm	Unifocal macro-PTC	Multifocal macro-PTC
	n = 182 (41.2%)	*n* = 19 (4.3%)	*n* = 47 (10.6%)	*n* = 141 (31.9%)	*n* = 53 (12.0%)		*P* value	*P* value	*P* value	*P* value
BRAF mutation[a]										
Absence	4 (14.8%)	0 (0.0%)	1 (12.5%)	2 (11.8%)	1 (12.5%)					
Presence	23 (85.2%)	4 (100.0%)	7 (87.5%)	15 (88.2%)	7 (87.5%)	0.878	1.000	1.000	1.000	1.000
ETE										
Absence	163 (89.6%)	19 (100.0%)	35 (74.5%)	121 (85.8%)	37 (69.8%)					
Minimal ETE	17 (9.3%)	0 (0.0%)	10 (21.3%)	13 (9.2%)	11 (20.8%)					
Gross ETE	2 (1.1%)	0 (0.0%)	2 (4.3%)	7 (5.0%)	5 (9.4%)	**0.001**	**0.006**	**0.023**	0.116	0.585
Vascular invasion										
Absence	177 (97.3%)	19 (100.0%)	46 (97.9%)	128 (90.8%)	47 (88.7%)					
Presence	5 (2.7%)	0 (0.0%)	1 (2.1%)	13 (9.2%)	6 (11.3%)	**0.014**	1.000	1.000	0.199	0.160
CLNM										
Absence	115 (63.2%)	14 (73.7%)	21 (44.7%)	51 (36.2%)	18 (34.0%)					
Presence	67 (36.8%)	5 (26.3%)	26 (55.3%)	90 (63.8%)	35 (66.0%)	**< 0.001**	**0.021**	**0.033**	0.299	0.273
LLNM										
Absence	173 (95.1%)	19 (100.0%)	40 (85.1%)	107 (75.9%)	38 (71.7%)					
Presence	9 (4.9%)	0 (0.0%)	7 (14.9%)	34 (24.1%)	15 (28.3%)	**< 0.001**	**0.039**	**0.024**	0.185	0.106

Bold values indicate $P<0.05$

PTC papillary thyroid carcinoma, *ETE* extrathyroidal extension, *CLNM* central lymph node metastasis, *LLNM* lateral lymph node metastasis, *TTD* total tumor diameter

[a]BRAF mutation analysis was started in 2017 and it was performed in 64 patients with PTC

Table 4 Associations between clinicopathological characteristics and CLNM in PTC patients

Clinicopathological characteristics	CLNM, no. (%)		*P* value	Multivariate analysis	
	Presence $n=223$ (50.5%)	Absence $n=219$ (49.5%)		Adjusted OR (95% CI)	*P* value
Sex					
Male	65 (29.1%)	44 (20.1%)		1	
Female	158 (70.9%)	175 (79.9%)	**0.027**	0.656 (0.401–1.072)	0.093
Age (year)					
≥ 45	92 (41.3%)	127 (58.0%)		1	
< 45	131 (58.7%)	92 (42.0%)	**< 0.001**	0.472 (0.309–0.719)	0.092
Primary tumor diameter (cm)					
≤ 1	98 (43.9%)	150 (68.5%)		1	
> 1	125 (56.1%)	69 (31.5%)	**< 0.001**	2.773 (1.880–4.091)	**< 0.001**
The number of foci					
1	157 (70.4%)	166 (75.8%)		1	
2	44 (19.7%)	47 (21.5%)		0.978 (0.589–1.623)	0.931
3	15 (6.7%)	5 (2.3%)		2.528 (0.839–7.617)	0.099
4	7 (3.1%)	1 (0.5%)	**0.014**	4.340 (0.453–41.622)	0.203
Multifocality					
Absence	157 (70.4%)	166 (75.8%)			
Presence	66 (29.6%)	53 (24.2%)	0.201		
Subgroup analysis by TTD and focality					
Unifocal micro-PTC	67 (30.0%)	115 (52.5%)		1	
Multifocal micro-PTC with TTD ≤ 1 cm	5 (2.2%)	14 (6.4%)		0.569 (0.191–1.692)	0.311
Multifocal micro-PTC with TTD > 1 cm	26 (11.7%)	21 (9.6%)		2.056 (1.019–4.147)	**0.044**
Unifocal macro-PTC	90 (40.4%)	51 (23.3%)		2.436 (1.483–4.000)	**< 0.001**
Multifocal macro-PTC	35 (15.7%)	18 (8.2%)	**< 0.001**	2.430 (1.194–4.944)	**< 0.001**
BRAF mutation[a]					
Absence	4 (10.5%)	4 (15.4%)			
Presence	34 (89.5%)	22 (84.6%)	0.847		
ETE					
Absence	169 (75.8%)	206 (94.1%)		1	
Minimal ETE	42 (18.8%)	9 (4.1%)		2.124 (1.419–3.179)	**< 0.001**
Gross ETE	12 (5.4%)	4 (1.8%)	**< 0.001**	1.713 (1.076–2.729)	**0.023**
Vascular invasion					
Absence	203 (91.0%)	214 (97.7%)		1	
Presence	20 (9.0%)	5 (2.3%)	**0.002**	1.255 (0.345–4.572)	0.730
LLNM					
Absence	168 (75.3%)	209 (95.4%)		1	
Presence	55 (24.7%)	10 (4.6%)	**< 0.001**	4.279 (2.028–9.028)	**< 0.001**

Bold values indicate $P<0.05$

PTC papillary thyroid carcinoma, *CLNM* central lymph node metastasis, *LLNM* lateral lymph node metastasis, *ETE* extrathyroidal extension, *TTD* total tumor diameter, *OR* odds ratio, *95% CI* 95% confidence interval

[a]BRAF mutation analysis was started in 2017 and it was performed in 64 patients with PTC

> 1 cm, ETE, vascular invasion and CLNM were significantly associated with LLNM (all $P<0.050$).

According to the multivariate analysis, primary tumor diameter > 1 cm (adjusted OR 4.900, $P<0.001$), unifocal macro-PTC (adjusted OR: 4.475, $P<0.001$), multifocal macro-PTC (adjusted OR 4.935, $P=0.001$), the presence of gross ETE (adjusted OR 6.178, $P<0.001$) and the presence of CLNM (adjusted OR 4.481, $P<0.001$) were all independent predictive factors for LLNM.

Table 5 Associations between clinicopathological characteristics and LLNM in PTC patients

Clinicopathological characteristics	LLNM, no. (%)		*P* value	Multivariate analysis	
	Presence $n=65$ (14.7%)	Absence $n=377$ (85.3%)		Adjusted OR (95% CI)	*P* value
Sex					
Male	18 (27.7%)	91 (24.1%)			
Female	47 (72.3%)	286 (75.9%)	0.539		
Age (year)					
≥45	27 (41.5%)	192 (50.9%)			
<45	38 (58.5%)	185 (49.1%)	0.162		
Primary tumor diameter (cm)					
≤1	16 (24.6%)	232 (61.5%)		1	
>1	49 (75.4%)	145 (38.5%)	**<0.001**	4.900 (2.686–8.940)	**<0.001**
The number of foci					
1	43 (66.2%)	280 (74.3%)			
2	13 (20.0%)	78 (20.7%)			
3	5 (7.7%)	15 (4.0%)			
4	4 (6.2%)	4 (1.1%)	0.058		
Multifocality					
Absence	43 (66.2%)	280 (74.3%)			
Presence	22 (33.8%)	97 (25.7%)	0.173		
Subgroup analysis by TTD and focality					
Unifocal micro-PTC	9 (13.8%)	173 (45.9%)		1	
Multifocal micro-PTC with TTD ≤1 cm	0 (0.0%)	19 (5.0%)		0.000 (0.000–0.000)	0.998
Multifocal micro-PTC with TTD >1 cm	7 (10.8%)	40 (10.6%)		2.693 (0.917–7.912)	0.072
Unifocal macro-PTC	34 (52.3%)	107 (28.4%)		4.475 (2.017–9.929)	**<0.001**
Multifocal macro-PTC	15 (23.1%)	38 (10.1%)	**<0.001**	4.935 (1.931–12.615)	**0.001**
BRAF mutation[a]					
Absence	2 (13.3%)	6 (12.2%)			
Presence	13 (86.7%)	43 (87.8%)	1.000		
ETE					
Absence	44 (67.7%)	331 (87.8%)		1	
Minimal ETE	8 (12.3%)	43 (11.4%)		1.293 (0.692–2.414)	0.421
Gross ETE	13 (20.0%)	3 (0.8%)	**<0.001**	6.178 (2.840–13.442)	**<0.001**
Vascular invasion					
Absence	57 (87.7%)	360 (95.5%)		1	
Presence	8 (12.3%)	17 (4.5%)	**0.026**	1.119 (0.369–3.391)	0.842
CLNM					
Absence	10 (15.4%)	209 (55.4%)		1	
Presence	55 (84.6%)	168 (44.6%)	**<0.001**	4.481 (2.158–9.307)	**<0.001**

Bold values indicate $P<0.05$

PTC papillary thyroid carcinoma, *CLNM* central lymph node metastasis, *LLNM* lateral lymph node metastasis, *ETE* extrathyroidal extension, *TTD* total tumor diameter, *OR* odds ratio, *95% CI* 95% confidence interval

[a]BRAF mutation analysis was started in 2017 and it was performed in 64 patients with PTC

Risk factors for RFS

We compared the RFS of different groups (Fig. 1, Table 6). The RFS did not show the significant difference between unifocal micro-PTC and multifocal micro-PTC with TTD ≤1 cm ($P=0.696$). Difference was not observed in the comparison of multifocal micro-PTC with TTD >1 cm, unifocal macro-PTC and multifocal macro-PTC (all $P>0.05$). However, when comparing multifocal micro-PTC with TTD >1 cm to unifocal micro-PTC or multifocal micro-PTC with TTD ≤1 cm, statistically significant difference could be found ($P=0.041$, $P=0.048$, respectively).

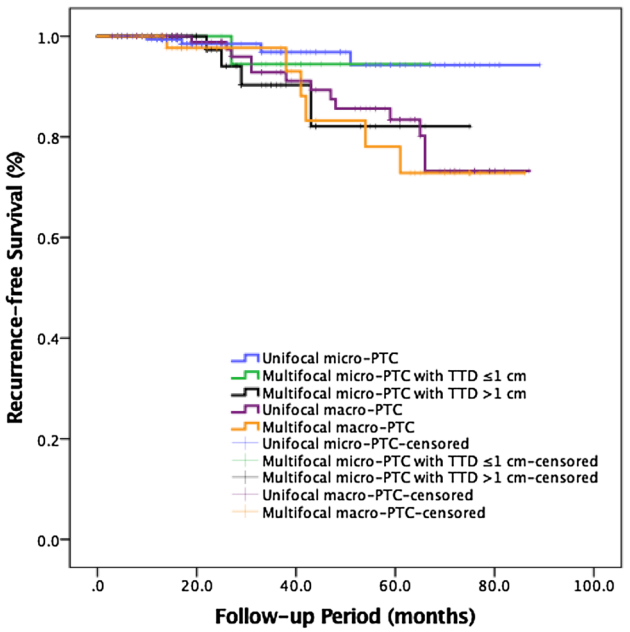

Fig. 1 Kaplan–Meier analysis of recurrence-free survival of unifocal micro-PTC, multifocal micro-PTC with TTD ≤ 1 cm, multifocal micro-PTC with TTD > 1 cm, unifocal macro-PTC, and multifocal macro-PTC

Univariate analysis in relation to RFS was conducted to determine the single variable which influenced the recurrence (Table 7). Multifocal micro-PTC with TTD > 1 cm, unifocal macro-PTC, multifocal macro-PTC, the presence of minimal ETE, the presence of gross ETE and the presence of CLNM were significantly associated with poor RFS (all $P < 0.05$).

Multivariate analysis with above significant factors showed that the presence of gross ETE (HR:5.640, $P = 0.015$) and the presence of CLNM (HR 2.798, $P = 0.010$) were independent predictors of poor RFS.

Discussion

Different from previous studies on effect of largest tumor size, we analyzed the effect of TTD on multifocal PTC patients. We found TTD is not only an effective indicator for clinicopathologic features, but also associated with RFS. Multifocal is a common finding in clinical practice, which accounted for 20.0% and 36.1% of PTC patients [4–6]. Despite the multifocality was widely evaluated previously, the prognostic significance of multifocality in PTC remains controversial [21]. For example, some studies demonstrated that multifocality was a risk factor for aggressive features of PTC [9, 10, 22, 23], but many tumor staging systems did not regard the multifocality as a high-risk feature or a parameter that determine the management for thyroid tumor [11, 12]. In our study, multifocality was related to the risk of ETE, which was similar with the finding of Genpeng et al. [22]. We further hypothesized that the characteristics of multifocal tumors may vary depending on the number of tumor lesions. As we expected, we observed that a higher number of PTC foci was associated with more aggressive features, such as more frequent CLNM. This finding was consistent with Al Afif et al. [9]. However, different from the findings of Kim et al. [10], our results showed that the number of foci was not associated with LLNM. Apart from the ethnic, regional, and clinical diversity, one of the leading causes of this result might be the differences in tumor diameter. Because the tumor diameter was related to ETE and LNM [24, 25], and the tumor diameter in our study was smaller than that of Kim et al. (1.23±0.93 cm vs. 1.6±1.2 cm, respectively), these might lead to the increased risk of LLNM in multifocal patients in the study of Kim et al.

Now, tumor size has become the important factor for predicting the prognosis. For example, primary tumor (T) stage is determined according to tumor size and ETE in AJCC TNM classification [13]. Moreover, several studies have proven that a larger tumor size was associated with poor

Table 6 Pairwise comparison of recurrence-free survival between different tumor groups

Subgroup analysis by TTD and focality	Unifocal micro-PTC	Multifocal micro-PTC with TTD ≤ 1 cm	Multifocal micro-PTC with TTD > 1 cm	Unifocal macro-PTC	Multifocal macro-PTC
	P value	*P* value	*P* value	*P* value	*P* value
Unifocal micro-PTC	–	0.696	**0.041**	**0.036**	**0.025**
Multifocal micro-PTC with TTD ≤ 1 cm	0.696	–	**0.048**	**0.039**	**0.030**
Multifocal micro-PTC with TTD > 1 cm	**0.041**	**0.048**	–	0.670	0.685
Unifocal macro-PTC	**0.036**	**0.039**	0.670	–	0.957
Multifocal macro-PTC	**0.025**	**0.030**	0.685	0.957	–

Bold values indicate $P<0.05$

TTD total tumor diameter

Table 7 Cox proportional hazards model demonstrating factors associated with recurrence-free survival in PTC patients

Variable	Univariate		Multivariate	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Sex				
Male	1			
Female	1.023 (0.450–2.324)	0.956		
Age (year)				
≥ 45	1			
< 45	1.326 (0.622–2.828)	0.465		
Primary tumor diameter (cm)				
≤ 1	1			
> 1	1.051 (0.425–2.604)	0.914		
The number of foci				
1	1			
2	1.216 (0.477–3.098)	0.682		
3	2.945 (0.990–8.761)	0.052		
4	2.995 (0.396–22.624)	0.288		
Subgroup analysis by TTD and focality				
Unifocal micro-PTC	1		1	
Multifocal micro-PTC with TTD ≤ 1 cm	1.690 (0.187–15.269)	0.641	2.569 (0.278–23.698)	0.405
Multifocal micro-PTC with TTD > 1 cm	3.058 (0.996–9.390)	**0.033**	2.296 (0.742–7.101)	0.149
Unifocal macro-PTC	3.798 (0.941–15.328)	**0.049**	3.117 (0.774–12.550)	0.110
Multifocal macro-PTC	3.786 (1.066–13.451)	**0.040**	1.985 (0.546–7.219)	0.298
Multifocality				
Absence	1			
Presence	1.387 (0.617–3.118)	0.429		
ETE				
Absence	1		1	
Minimal ETE	3.728 (1.225–11.339)	**0.020**	2.217 (0.560–8.777)	0.257
Gross ETE	5.562 (1.370–22.581)	**0.016**	5.640 (1.403–22.674)	**0.015**
Vascular invasion				
Absence	1			
Presence	2.366 (0.919–6.093)	0.074		
CLNM				
Absence	1		1	
Presence	3.222 (1.037–10.009)	**0.043**	2.798 (1.274–6.145)	**0.010**
LLNM				
Absence	1			
Presence	1.201 (0.473–3.045)	0.700		
Treatment				
Thyroid lobectomy without RAI	1			
Thyroid lobectomy with RAI	1.200 (0.670–2.150)	0.540		
Total thyroidectomy without RAI	1.196 (0.665–2.151)	0.550		
Total thyroidectomy with RAI	2.126 (0.884–5.114)	0.092		
Title of surgeon				
Deputy chief physician	1			
Chief physician	0.708 (0.365–1.377)	0.309		

Bold values indicate $P<0.05$

PTC papillary thyroid carcinoma, *TTD* total tumor diameter, *ETE* extrathyroidal extension, *CLNM* central lymph node metastasis, *LLNM* lateral lymph node metastasis, *CND* central neck dissection, *LND* lateral neck dissection, *RAI* radioactive iodine, *HR* hazard ratio, *CI* confidence intervals

survival and a higher recurrence rate [26–29]. Tumor size is the size of largest tumor in multifocal PTC, the effect of other tumor foci on aggressiveness has not been fully studied. Assessing the largest tumor size and ignoring the other foci in multifocal tumors might underestimate the clinicopathologic features of tumors, leading to inaccurate tumor stage and affecting the treatment. Thus, an additional parameter, TTD, was recognized as the tool that could be used to assess the all foci in multifocal tumors. The role of TTD in multifocal PTC has been investigated in some research. For example, the proportions of CLNM (Zhao et al. [14] and Liu et al. [15]) and ETE (Liu et al. [15]) in multifocal micro-PTC with TTD > 1 cm were significantly higher than unifocal micro-PTC, but were similar with unifocal macro-PTC. Different from previous studies, apart from the CLNM and ETE, we also investigated the association between TTD and other characteristics (such as LLNM, vascular invasion and BRAF mutations) to further identify the aggressiveness of other foci. To our surprise, apart from the CLNM and ETE, LLNM rate was also significantly higher in multifocal micro-PTC with TTD > 1 cm than in unifocal micro-PTC or multifocal micro-PTC with TTD ≤ 1 cm. However, when compared to unifocal macro-PTC or multifocal macro-PTC, multifocal micro-PTC with TTD > 1 cm did not show any significant difference in terms of clinicopathologic features. This result was consistent with the study of Luo et al. [30] that the probability of CLNM and LLNM increased with the increase of the sum of the maximum diameter of multifocal micro-PTC. Our finding reflected that multifocal micro-PTC tend to behave like the macro-PTC once the TTD exceeded 1.0 cm. In another word, the size of other foci should not be neglected, because the TTD might be the true size of multifocal micro-PTC.

Given multifocal micro-PTC with TTD > 1 cm having aggressive clinicopathologic features, we wonder if multifocal micro-PTC with TTD > 1 cm is associated with worse outcomes. Therefore, we further investigate the prognosis of patients grouped by TTD and focality. As the Kaplan–Meier analysis revealed, the RFS was significant higher in unifocal micro-PTC or multifocal micro-PTC with TTD ≤ 1 cm than in multifocal micro-PTC with TTD > 1 cm. However, the RFS did not significantly differ between multifocal micro-PTC with TTD > 1 cm and macro-PTC. Moreover, after investigating the risk factors of RFS, we found multifocal micro-PTC with TTD > 1 cm had the 3.508 ($P = 0.033$) times higher risk of recurrence than unifocal micro-PTC. Considering the poor prognosis and aggressive clinicopathologic features of multifocal micro-PTC with TTD > 1 cm, we recommend the treatment for these patients should be distinct from unifocal micro-PTC and multifocal micro-PTC with TTD ≤ 1 cm. Active surveillance can be considered as an alternative to immediate surgery in low-risk micro-PTC according to the ATA guidelines (2015) [11]. In contrast to surgery, active surveillance has the advantage in less adverse events (mainly surgical complications) and medical costs [31]. The criteria for determining active surveillance candidates in micro-PTC depend extensively on the accuracy of imaging, especially US. However, US has the limitation in detecting LNM and gross ETE [32]. Moreover, patients and clinicians were all worried about the delaying immediate treatment which may result in more extensive surgical intervention. For micro-PTC with TTD ≤ 1 cm, we still suggest the immediate surgery. As for the optimal surgical treatment strategy, especially whether the prophylactic CND should be performed in cN0 patients remains debatable. According to the ATA guidelines (2015) [11], for cN0 PTC patients with advanced primary tumors (T3 or T4), the prophylactic CND was recommended, while for cN0 PTC patients with T1 or T2 tumors, thyroidectomy was sufficient. In view of the significant complications (such as recurrent laryngeal nerve damage and persistent hypoparathyroidism) caused by the reoperation for recurrence of the central compartment, Japanese Society of Thyroid Surgeons (JSTS) recommend to routinely perform the prophylactic CND [33]. After analyzing the risk factors of CLNM, we found that multifocal micro-PTC with TTD > 1 cm, similar to unifocal macro-PTC and multifocal macro-PTC, was also an independent risk factor for CLNM. Moreover, consistent with previous studies [29, 34], we found that the presence of CLNM was not only an independent risk factor for RFS, but also increased the risk of recurrence. In view of the high recurrence rate of patients with TTD > 1 cm and the risks associated with the second surgery, we recommend that the treatment of multifocal micro-PTC with TTD > 1 cm should be the same as the macro-PTC, which means the prophylactic CND should be routinely performed in multifocal micro-PTC with TTD > 1 cm to improve the prognosis. Because unifocal micro-PTC and multifocal micro-PTC with TTD ≤ 1 cm were not risk factors for CLNM and RFS, for these patients without LNM detected preoperatively, thyroidectomy/TT without the prophylactic CND would be sufficient. From the perspective of survival and quality of life, we agreed with ATA guidelines (2015) that LND should only be performed when LNM was detected in the lateral compartment [11].

Our study has several limitations. The main limitation of our study is its retrospective in nature. Second, the ATA guidelines did not advocate the routinely prophylactic CND [11], which might be the weak point of our cohort. Moreover, considering the potential complications and ethical issues, LND was not performed in all patients. Hence, undetected LLNM may exist. Third, although there were high numbers of patients included, sample sizes decreased when we divided patients into different groups according to multifocality and TTD. Lastly, average follow-up period was 43 months in our study, which might lead to the low recurrence rates. Longer follow-up period may reveal an increase

or difference in recurrence rates between different groups. Therefore, our findings could be improved by the multicenter prospective study with large sample size.

In conclusion, for multifocal micro-PTC, the TTD can better assess the aggressiveness of the tumor. To some extent, TTD should be considered as the true tumor size of multifocal PTC rather than the largest diameter. Multifocal micro-PTC with TTD > 1 cm was similar with macro-PTC not only in terms of clinicopathologic features, but also in terms of prognosis. Hence, we recommend the treatment of multifocal micro-PTC with TTD > 1 cm should be the same as the macro-PT to improve prognosis.

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Compliance with ethical standards

Conflicts of interest This manuscript has not been published nor submitted for publication elsewhere. All authors have contributed significantly, and agree with the content of the manuscript. The authors reported no proprietary or commercial interest in any product mentioned or concept discussed in this article.

Ethical approval This study has been approved by the Institutional Review Board of Changzhou First People's Hospital ethics committee, and has been performed according to the ethical standards laid down in the 1964 Declaration of Helsinki.

Informed consent Informed consent was obtained from all individual participants included in the study.

References

1. Lim H, Devesa SS, Sosa JA et al (2017) Trends in thyroid cancer incidence and mortality in the United States, 1974–2013. JAMA 317(13):1338–1348
2. Morris LGT, Sikora AG, Tosteson TD et al (2013) The increasing incidence of thyroid cancer: the influence of access to care. Thyroid 23(7):885–891
3. Kim SH, Roh JL, Gong G et al (2016) Differences in the recurrence and survival of patients with symptomatic and asymptomatic papillary thyroid carcinoma: an observational study of 11,265 person-years of follow-up. Thyroid 26(10):1472–1479
4. So YK, Kim MW, Son YI (2015) Multifocality and bilaterality of papillary thyroid microcarcinoma. Clin Exp Otorhinolaryngol 8(2):174–178
5. Ng SC, Kuo SF, Chen ST et al (2017) Therapeutic outcomes of patients with multifocal papillary thyroid microcarcinomas and larger tumors. Int J Endocrinol. 2017:4208178
6. Kuo SF, Lin SF, Chao TC et al (2013) Prognosis of multifocal papillary thyroid carcinoma. Int J Endocrinol 2013:809382
7. Qu N, Zhang L, Ji QH et al (2014) Number of tumor foci predicts prognosis in papillary thyroid cancer. BMC Cancer 14:914
8. Kim HJ, Sohn SY, Jang HW et al (2013) Multifocality, but not bilaterality, is a predictor of disease recurrence/persistence of papillary thyroid carcinoma. World J Surg 37(2):376–384
9. Al Afif A, Williams BA, Rigby MH et al (2015) Multifocal papillary thyroid cancer increases the risk of central lymph node metastasis. Thyroid 25(9):1008–1012
10. Kim HJ, Park HK, Byun DW et al (2015) Number of tumor foci as predictor of lateral lymph node metastasis in papillary thyroid carcinoma. Head Neck 37(5):650–654
11. Haugen BR, Alexander EK, Bible KC et al (2016) 2015 American Thyroid Association Management guidelines for adult patients with thyroid nodules and differentiated thyroid cancer: the American Thyroid Association Guidelines Task Force on Thyroid Nodules and Differentiated Thyroid Cancer[J]. Thyroid 26(1):1–133
12. Pacini F, Schlumberger M, Dralle H et al (2006) European consensus for the management of patients with differentiated thyroid carcinoma of the follicular epithelium. Eur J Endocrinol 154(6):787–803
13. Amin MB, Edge SB, Greene FL et al (2017) AJCC cancer staging manual, 8th edn. Springer, New York, pp 873–890
14. Zhao Q, Ming J, Liu C et al (2013) Multifocality and total tumor diameter predict central neck lymph node metastases in papillary thyroid microcarcinoma. Ann Surg Oncol 20(3):746–752
15. Liu C, Wang S, Zeng W et al (2017) Total tumour diameter is superior to unifocal diameter as a predictor of papillary thyroid microcarcinoma prognosis. Sci Rep 7(1):1846
16. Jr SB, Ferris RL, Goldenberg D et al (2012) American Thyroid Association consensus review and statement regarding the anatomy, terminology, and rationale for lateral neck dissection in differentiated thyroid cancer. Thyroid 22(5):501
17. Carty SE, Cooper DS, Doherty GM et al (2009) Consensus statement on the terminology and classification of central neck dissection for thyroid cancer. Thyroid 19(11):1153–1158
18. Durante C, Montesano T, Torlontano M et al (2013) Papillary thyroid cancer: time course of recurrences during postsurgery surveillance. J Clin Endocrinol Metab 98(2):636–642
19. Grant CS (2015) Recurrence of papillary thyroid cancer after optimized surgery. Gland Surg 4(1):52–62
20. Tuttle RM, Tala H, Shah J et al (2010) Estimating risk of recurrence in differentiated thyroid cancer after total thyroidectomy and radioactive iodine remnant ablation: using response to therapy variables to modify the initial risk estimates predicted by the new American Thyroid Association staging system. Thyroid 20(12):1341–1349
21. Iacobone M, Jansson S, Barczynski M et al (2014) Multifocal papillary thyroid carcinoma—a consensus report of the European Society of Endocrine Surgeons (ESES)[J]. Langenbecks Arch Surg 399(2):141–154
22. Genpeng L, Jianyong L, Jiaying Y et al (2018) Independent predictors and lymph node metastasis characteristics of multifocal papillary thyroid cancer. Medicine (Baltimore) 97(5):e9619
23. Gui CY, Qiu SL, Peng ZH et al (2018) Clinical and pathologic predictors of central lymph node metastasis in papillary thyroid microcarcinoma: a retrospective cohort study. J Endocrinol Invest 41(4):403–409
24. Liu L, Oh C, Heo JH et al (2018) Clinical significance of extrathyroidal extension according to primary tumor size in papillary thyroid carcinoma. Eur J Surg Oncol 44(11):1754–1759
25. Can N, Tastekin E, Ozyilmaz F et al (2015) Histopathological evidence of lymph node metastasis in papillary thyroid carcinoma. Endocr Pathol 26(3):218–228
26. Bilimoria KY, Bentrem DJ, Ko CY et al (2007) Extent of surgery affects survival for papillary thyroid cancer. Ann Surg. 246(3):375–381 **(discussion 374–381)**

27. Rajjoub SR, Yan H, Calcatera NA et al (2018) Thyroid lobectomy is not sufficient for T2 papillary thyroid cancers. Surgery 163(5):1134–1143
28. Untch BR, Palmer FL, Ganly I et al (2014) Oncologic outcomes after completion thyroidectomy for patients with well-differentiated thyroid carcinoma. Ann Surg Oncol 21(4):1374–1378
29. Nguyen XV, Roy Choudhury K, Tessler FN et al (2018) Effect of tumor size on risk of metastatic disease and survival for thyroid cancer: implications for biopsy guidelines. Thyroid 28(3):295–300
30. Luo Y, Zhao Y, Chen K et al (2019) Clinical analysis of cervical lymph node metastasis risk factors in patients with papillary thyroid microcarcinoma. J Endocrinol Invest 42(2):227–236
31. Miyauchi A, Ito Y, Oda H (2018) Insights into the management of papillary microcarcinoma of the thyroid. Thyroid 28(1):23–31
32. Hwang HS, Orloff LA (2011) Efficacy of preoperative neck ultrasound in the detection of cervical lymph node metastasis from thyroid cancer. Laryngoscope 121(3):487–491
33. Takami H, Ito Y, Okamoto T et al (2011) Therapeutic strategy for differentiated thyroid carcinoma in Japan based on a newly established guideline managed by Japanese Society of Thyroid Surgeons and Japanese Association of Endocrine Surgeons. World J Surg 35(1):111–121
34. Cho SY, Lee TH, Ku YH et al (2015) Central lymph node metastasis in papillary thyroid microcarcinoma can be stratified according to the number, the size of metastatic foci, and the presence of desmoplasia. Surgery 157(1):111–118