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Preoperative risk factors and recommendations for surgical intervention in cN0 papillary thyroid microcarcinoma

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The evaluation and management of papillary thyroid microcarcinoma (PTMC) have always been challenging and controversial. Our retrospective study aimed to investigate the metastatic trend and risk factors of cN0 papillary thyroid microcarcinoma patients and provide advice for surgical strategies. The clinicopathological features of 556 cN0 PTMC patients undergoing thyroidectomy combined with central compartment dissection (CCD) were compared by the χ^2 test and risk factors were identified by binary logistic regression analysis. Numbers of dissected lymph nodes (DLN) and metastatic lymph nodes (MLN) were analyzed using the Mann-Whitney U test to compare metastatic trends between different lobes. Male gender, tumor maximum diameter (TMD) larger than 5 mm, multifocality, and capsular/extracapsular invasion were metastatic risk factors of central compartment metastasis (CCM) ($p<0.05$). The number of DLN in the right level VI was larger than in the left ($p<0.05$), while the number of MLN was similar ($p>0.05$). The chance of CCM was higher when the number of DLN was larger than 5 ($p<0.05$). After identified metastatic trends and risk factors, we recommend surgery for patients deciding on aggressive treatment, especially for cases where a combination of risk factors is present. And to ensure no residual metastatic lymph nodes and reduce secondary surgery rates, adequate lymphadenectomy on the diseased side would be a better choice considering the standard of care.

Key words: papillary thyroid microcarcinoma, PTMC, lymphadenectomy, lymph node metastasis, risk factor, surgery

PTMCs are defined as papillary thyroid tumors with a maximum diameter of no more than 10 mm, present with or without cervical lymph node metastasis [1]. Increasing awareness of thyroid-related disease together with improvements in imaging and pathology has seen PTMCs evolve into a higher proportion of diagnosed thyroid malignancies. Nonetheless, the reported 10-year survival rate of PTMC is up to 99% [2]. In contrast to the excellent prognosis, lymph node metastasis and multifocality are commonly seen after pathological assessment [3–5]. In recent years, the treatment of PTMC cases without the nodal regional disease (cN0) has been controversial, with surgery, active surveillance, and thermal ablation all considered viable treatment choices [6–8]. It is therefore imperative to know whether the surgery instead of conservative treatment can provide cN0 PTMC patients with the best outcome.

Towards addressing this question, we retrospectively analyzed a large cohort of cN0 PTMC patients who underwent CCD. Evaluating the associations between preoperative clinical variables and pathologically confirmed metastasis identified several independent risk factors for metastasis, which help advise the decision to undertake surgery.

Patients and methods

Patients. A total of 556 consecutive PTMC patients treated at the Head and Neck Surgery Department, Fujian Cancer Hospital between June 2018 and December 2019 were selected for the retrospective review. The inclusion criteria involved: 1) no signs of lymph node metastasis on preoperative examination, 2) pathological confirmation as PTMC, 3) surgical treatment involving thyroidectomy combined with unilateral or bilateral CCD, 4) no evidence of lateral neck metastasis, 5) no medical history of thyroid-associated medication or prior thyroid surgery. The average age of the 409 females and 147 males was 45.7±10.7 years. Other clinicopathologic features recorded including tumor location, TMD, multifocality, capsular/extracapsular invasion, lymph node location, number of DLN, number of MLN, and postoperative follow-up were collected.

Thyroidectomy. Operations were performed by surgeons from a single treatment group to ensure consistent surgical strategies. Intraoperative frozen sections were undertaken for all patients and once nodule malignancy was confirmed, CCD was performed on the malignant side (to level VI including right VIb). The study was approved by the Ethics Committee of Fujian Cancer Hospital with informed signed consent taken from patients and immediate family members before the operation.

Table 1. Patient characteristics.

Characteristics	n, (%)
Gender	
Male	147 (26.4)
Female	409 (73.6)
Age at diagnosis	
<55	437 (78.6)
≥55	119 (21.4)
Tumor Location*	
Right Lobe	230 (41.4)
Left Lobe	312 (56.1)
Both Lobes	14 (2.5)
Tumor Maximum Diameter (mm)	
≤5	271 (48.7)
5< TMD ≤10	285 (51.3)
Number of Lymph Nodes Dissected *	
≤5	288 (50.5)
5< LND ≤10	205 (36.0)
>10	77 (13.5)
N stage	
pN0	320 (57.6)
pN1a	236 (42.4)

Note: *tumor on both lobes were counted as left and right level VI separately

Table 2. Metastatic risk factors of PTMC patients.

Category	Cases (%)	CCM [number (%)]		χ^2	p-value
		CCM	Non-CCM		
Gender				8.074	0.004
Male	147 (26.4)	77 (52.4)	70 (47.6)		
Female	409 (73.6)	159 (38.9)	250 (61.1)		
Age at diagnosis				2.469	0.116
<55	437 (78.6)	193 (44.2)	244 (55.8)		
≥55	119 (21.4)	43 (36.1)	76 (63.9)		
TMD (mm)				6.656	0.010
≤5 mm	271 (48.7)	100 (36.9)	171 (63.1)		
5< TMD ≤10	285 (51.3)	136 (47.7)	149 (52.3)		
Multifocality				10.899	0.001
No	368 (66.2)	138 (37.5)	230 (62.5)		
Yes	188 (33.8)	98 (52.1)	90 (47.9)		
Capsular/Extra-capsular invasion				6.485	0.011
No	399 (71.8)	156 (39.1)	243 (60.9)		
Yes	157 (28.2)	80 (51.0)	77 (49.0)		

Statistical analysis. All statistical analyses were performed using IBM SPSS statistics v24.0 with descriptive statistics were presented as summarized data. Continuous variables were expressed as number (%) or $\bar{x}\pm s$ and compared using the Mann-Whitney U-test. Numeric variables were analyzed by χ^2 test and risk factors were identified by binary logistic regression analysis based on the results. A p-value <0.05 was considered as statistically significant.

Results

Amongst 556 cases, the mean TMD was 0.57±0.21 mm. Preoperative examination revealed 117 patients with multifocality with 76 of these cases exhibiting capsular/extracapsular invasion. The tumor distribution to the left and right lobes was 56.1% and 41.4%, respectively, with 2.5% of cases involving both lobes. CCM was found in 236 of 556 patients (42.4%). Four patients had temporary post-operative hypocalcemia (1 recovered in 3 days, 3 in 2 weeks), and 1 patient suffered temporary hoarseness (recovered after 9 weeks). Post-surgical follow-up was 12–18 months after surgery, 8 of them lost follow-up (1 in 3 months, 1 in 9 months, 5 in 15 months, 1 in 18 months). No recurrences were found after follow-up. All patient characteristics are summarized in Table 1.

Patient clinicopathological features were first applied to a multivariate model to identify metastatic risk factors. This analysis revealed that CCM was significantly associated with male gender, TMD larger than 5 mm, multifocality, and capsular/extracapsular invasion (χ^2 test, $p<0.05$). However, age of diagnosis made no impact on CCM (p=0.116, Table 2).

We then applied binary logistic regression analysis to define which multivariate variables served as independent risk factors. Here this analysis showed that gender (OR=1.688), TMD larger than 5 mm (OR=1.562), and multifocality (OR=1.914) were all independent risk factors for CCM ($p<0.05$, Table 3). According to these criteria, only 27 of all patients were objectively assessed as "low-risk" (female, TMD ≤5 mm, uni-focality, and without capsular/extracapsular invasion).

We then turned to evaluate lymph node metastasis, comparing nodal status on different sides. Here the average DLN and MLN values on the right (level VI) were 6.8±4.6 and 1.0±1.9, respectively, whereas for the left side these were 5.6±3.8 and 0.9±1.8, respectively. Dissected lymph node numbers on the right were significantly more than on

Table 3. Binary logistic regression analysis for metastatic risk factors.

Category	OR (95% CI)	p-value
Gender	1.688 (1.141–2.497)	0.009
Tumor maximum diameter	1.562 (1.102–2.214)	0.012
Multifocality	1.914 (1.326–2.762)	0.001

the left side (p=0.001), although the average MLN detected were similar (p=0.188, Table 4). We found there was a higher chance of CCM when the number of DLN was more than 5 (p=0.004), although the tumor location did not make an impact (p=0.128, Table 5).

Table 4. Comparison of lymph nodes trend in different levels. *

Category	Lymph nodes number or metastatic ratio	Z	p-value
Lymph Nodes Dissected		3.199	0.001
Right level VI	6.83±4.582		
Left level VI	5.64±3.813		
Lymph Nodes Metastasis		1.317	0.188
Right level VI	1.00±1.928		
Left level VI	0.89±1.769		

Note: *tumor on both lobes were counted as left and right level VI separately

Table 5. Relation of CCM and lymph node dissected number. *

Category	Cases (%)	CCM [number (%)]		χ^2	p-value
		CCM	Non-CCM		
Number of DLN				10.883	0.004
≤5	288 (50.5)	88 (30.6)	200 (69.4)		
5< LND ≤10	205 (36.0)	87 (42.4)	118 (57.6)		
>10	77 (13.5)	36 (46.8)	41 (53.2)		
Tumor location				2.314	0.128
Right lobe	244 (42.8)	99 (40.6)	145 (59.4)		
Left lobe	326 (57.2)	112 (34.4)	214 (65.6)		

Note: *tumor on both lobes were counted as left and right level VI separately

Discussion

Slow disease progression and good prognosis of PTMC have long generated controversy about its best treatment options. Ito and colleagues [9] suggested that low-risk PTMC can be placed under active surveillance, and moreover, ATA guidelines for thyroid nodules and differentiated thyroid cancer do not recommend prophylactic lymphadenectomy for non-invasive, T1-2, and cN0 differentiated thyroid cancers [10]. Additionally, arguments both for and against thermal ablation of PTMC have been made [8, 11, 12]. Here we retrospectively investigated a cohort of cN0 patients opting for surgery. Through analysis of different clinicopathologic features and metastatic trends, we aimed to define the risks and benefits of the surgical strategy.

First, consistent with other research, male gender, multifocality, and capsular/extracapsular invasion were more likely to indicate the presence of lymph node metastasis [13, 14]. However, unlike previous reports, age of diagnosis was not identified as a risk factor, indicating that age should not be a judgment criterion for surgery or lymphadenectomy. However, we found that not all risk factors can be discovered through preoperative examination, thus emphasizing the importance of consistent active surveillance for low-risk cases to identify those requiring aggressive treatment. Notably, the chance of lymphatic metastasis was higher when TMD was larger than 5 mm (47.7% vs. 36.9%, p<0.05), implying that tumor size should be considered during the decision making for surgery or intraoperative lymphadenectomy. Consistently, the Chinese Expert Consensus for Papillary Thyroid Microcarcinoma recommends TMD ≥6 mm as a relative indication for surgery [15]. Thus, given the higher metastatic risk, more attention should be paid to PTMC patients with TMD >5 mm when a choice of active surveillance is made. If surgical treatment is planned, prophylactic lymph node dissection rather than lobectomy only would be preferred for larger tumor sizes.

One salient feature of our data concerned the high metastatic rate of cN0 cases (42.4%). Here we considered whether there was any asymmetrical bias between tumor site and metastasis. Although the number of lymph nodes dissected from right level VI was greater than the left, there were no differences in nodal metastasis between the two sides. The reason for the increased number of dissections on the right side is unclear, but nonetheless, both sides should be treated equally because of similar metastatic risk. Considering the central compartment includes level VIb nodes present in the deep previsceral space, lymphadenectomy should aim to adequately excise all involved lymph nodes.

We further considered the impact of the extent of nodal involvement. Dividing cases according to the number of DLN, we found CCM was more likely in cases where over 5 lymph nodes were dissected (range 0 to 28 nodes). Importantly, this finding does not indicate an incomplete lymphadenectomy where less than 5 nodes were dissected. Indeed, radical lymphadenectomy was performed as required, with 50.5% of cases having no more than 5 lymph nodes involved. Since lymph node metastasis increases the risk of recurrence [16–18], this highlights the importance of a complete CCD. The more adequate the lymphadenectomy, the better the likely outcome, thereby reducing the chance of secondary surgery, associated morbidity, and costs.

Most low-risk PTMC patients can be treated by active surveillance, but for those who do not accept conservative therapy or for high-risk cases, surgery is a reliable and effective management option. As seen in our study, there are inconsistent findings in MLN, tumor number, and capsular invasion between preoperative examination and pathological results. According to our experience, no patients undertaking prophylactic lymphadenectomy exhibited recurrences in 12–18 months follow-up. Moreover, the complications of surgery for PTMC are minimal and mostly temporary. Thermal ablation has also been reported to be effective and safe in 5-year follow-up studies [11, 19]. Nonetheless, given the long-life expectancy of PTMC patients, it would be expected that recurrences might occur after a long period of time. Concerns have also been raised about the restricted healing of thermal ablation where post-

operative tissue adhesion could cause extra difficulty in secondary surgery [12]. Therefore, although active surveillance is the first option for low-risk cN0 patients, we recommend surgery for patients deciding on aggressive treatment, especially for cases where a combination of risk factors is present. And to ensure no residual metastatic lymph nodes and reduce secondary surgery rates, adequate lymphadenectomy on the diseased side should be considered the standard of care. However, considering the differences in the accuracy of preoperative evaluation and the skills of surgical technique in different centers, safety and completeness should be balanced according to the situation. Due to the relatively short follow-up of 18 months, we have not been able to completely assess the adequacy of prophylactic lymphadenectomy on recurrence and survival rates. We continue to monitor this cohort and will report long-term follow-up in due course.

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