Risk factors for predicting central lymph node metastasis in papillary thyroid microcarcinoma (CN0): a study of 273 resections

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Abstract. – **OBJECTIVE:** The role of routine central lymph node dissection (CLND) for clinically central lymph node negative (CN0) papillary thyroid microcarcinoma (PTMC) remains uncertain. We aim to determine the predictive factors for central lymph node metastasis (CLNM) in papillary thyroid microcarcinoma.

PATIENTS AND METHODS: A total of 273 patients diagnosed with clinically central lymph node negative PTMC from 2014 to 2016 were included. The predictive risk factors for CLNM were analyzed with respect to age, sex, tumor size, tumor multifocal, lymphadenectasis of lateral neck, capsular invasion, extra capsular spread (ECS), coexistence of chronic lymphocytic thyroiditis (Hashimoto thyroiditis, HT) and nodular goiter (NG), BRAFV600E mutation and subtype of papillary thyroid carcinoma (PTC). Univariate and multivariate analyses were performed to identify the risk factors for CLNM.

RESULTS: Among the 273 patients, the CLNM occurred in 80 patients (29.3%). By univariate and multivariate analyses, tumor size (OR 2.07; *p*<0.001), multifocal (OR 2.67; *p*<0.004), lymphadenectasis of lateral neck (OR 9.28; *p*<0.001), tumor extent (OR 42.01; *p*<0.001) were independently correlated with CLNM. In further study, dorsal part of solitary lesion (OR: 16.312, 95%CI: 3.349-79.455, *p*=0.001), capsular invasion (OR: 42.012, 95% CI: 5.209-338.861, *p*<0.001), 6<D≤9 (OR: 8.400, 95% CI: 1.866-37.807, *p*=0.006) and D=1 (OR: 11.455, 95% CI: 2.500-52.480, *p*=0.002) were more tended to have CLNM.

CONCLUSIONS: A prophylactic central lymph node dissection should be considered particularly to PTMC patients with each of tumor size > 6 mm, dorsal part of solitary lesion, multifocal, lymphadenectasis of lateral neck and capsular invasion.

Key Words
   Papillary thyroid microcarcinoma, Lymph node metastasis, Tumor, CN0.

Introduction

According to the World Health Organization classification system for thyroid tumors, papillary thyroid microcarcinoma (PTMC) is defined as a papillary thyroid carcinoma (PTC) of which the greatest diameter is less than or equal to 1 cm[1]. With the continuous development of diagnostic imaging such as computed tomography, magnetic resonance imaging and ultra-sonography, the detection rate of PTMC has been increased[2]. Although PTMC has an indolent course, the cervical lymph node metastasis (CLNM) of PTMC was reported from 12.3 to 64.1% of patients. Moreover, it was associated with local recurrence and distant metastasis[3-5]. However, the role of routine central lymph node dissection (CLND) for PTMC remains uncertain according to no differences between CLND or not in prognosis[6]. In addition, CLND can raise the rate of postoperative hypocalcemia. Thus, better knowledge about the risk factors for CLNM may guide clinical decisions to regard which case requires CLND. The purpose of this study was to determine the risk factors predictive of CLNM in PTMC using a retrospective cohort study.

Patients and Methods

Patients

This retrospective cohort study consisted of 273 patients with PTMC who were treated in Nanjing Hospital of traditional Chinese Medicine from June 2014 to June 2016. This study was approved by the Ethics Committee of Nanjing Hos-

pital of Traditional Chinese Medicine. Signed written informed consents were obtained from all participants before the study. All of the 273 patients underwent US examination before operative to detect the size of tumor and presence of LNM. Patients with unilateral PTMC underwent total thyroidectomy (TT) or unilateral lobectomy plus isthmusectomy and ipsilateral central lymph node dissection (CLND). Patients with bilateral PTMC underwent TT and bilateral prophylactic CLND. Patients with isthmus PTMC underwent TT and bilateral prophylactic CLND. Lateral compartment lymph node dissection (LLND) was selectively performed if lymph node suspicious for metastases was found before or at the time of operation. All PTMCs were proved by histological diagnosis.

Methods

According to central compartment lymph node status, patients were divided into two groups: CLNM (+) group and CLNM (-) group. The association between CLNM and the clinical and pathological factors such as age (< 45 and ≥ 45), gender (female and male), tumor size ($0 < D \leq 3$, $3 < D \leq 6$, $6 < D \leq 9$, D = 1), location of the primary tumors (multifocal lesions, solitary lesion), tumor extent (within capsule, capsular invasion, ECS), accompanying disease (NG, HT), BRAF-V600E mutation and subtype of PTC (follicular variant, ordinary) were analyzed. Hypocalcemia was defined as total calcium < 8.0 mg/dL, corrected for serum albumin concentration. Permanent hypocalcemia was defined as a low total calcemia concentration requiring calcium supplementation for > 6 months after surgery. Postoperative vocal fold palsy, chyle leakage, and hematoma, were also investigated.

Statistical Analysis

The statistical analysis was performed using SPSS 17.0 (Version X; IBM, Armonk, NY, USA) software. x^2 test and Fisher's exact test were used to evaluate differences between qualitative variables. Logistic regression analysis was performed to identify the multivariate correlates of CLNM. The *p*-value of < 0.05 was considered statistically significant.

Table I. Characteristics of patients with papillary thyroid microcarcinoma.

Characteristics	No. (%)	Characteristics	No. (%)
Age (years)	43.7 ±13.1[a]	Tumor extent	28 (10.3)
< 45	166 (60.8)	Within capsule	253 (92.7)
≥ 45	107 (39.2)	Capsular invasion	17 (6.2)
Gender		ECS	3 (1.1)
Female	214 (78.4)	Accompanying disease	
Male	59 (21.6)	NG	
Tumor size		Present	63 (23.1)
0< D ≤3	30 (11.0)	Absent	210 (76.9)
3< D ≤6	103 (37.7)	HT	
6< D ≤9	80 (29.3)	Present	42 (15.4)
D = 1	60 (22.0)	Absent	231(84.6)
Location of the primary		BRAFV600E	
tumors		Positive	115 (42.1)
Multifocal lesions	111 (40.7)	Negative	158 (57.9)
In both lobes	61 (55.0)	Subtype	
In one lobe	44 (39.6)	Follicular variant	4 (1.5)
In isthmus and lobe	6 (5.4)	Ordinary	269 (98.5)
Solitary lesion	162 (59.3)	Lymphadenectasis of	
Isthmus	4 (2.4)	lateral neck	
Others	158 (97.5)	Present	36 (13.2)
Upper third	53 (33.5)[b]	Absent	237 (86.8)
Middle third	66 (41.8)[b]		
Lower third	39 (24.7)[b]		
Surface part	31 (19.6)[b]		
Middle part	93 (58.9)[b]		
Dorsal part	34 (21.5)[b]		

[a]Mean±standard deviation. [b]the total is 158. D: maximal diameter of lesion. ECS: extracapsular spread. NG: Nodular goiter. HT: Hashimoto's thyroiditis.

Results

The clinical and pathological characteristics were summarized in Table I. Among the 273 patients with PTMC treated in our hospital, there were 214 (78.4%) females and 59 (21.6 %) males at the mean age of 43.7 ± 13.1 years (range from 18 to 81 years). 162 (59.3%) patients had solitary lesion and 111 (40.7%) patients had multifocal lesions. 61 (55.0%) patients presented bilateral lesions. 28 (10.3%) patients were characterized by local infiltration. CLNM occurred in 80 (29.3%) patients. The prognostic results of papillary thyroid carcinoma were positive. Generally, patients can survive for more than 10 years. During the follow-up, no patient died. By univariate analysis, CLNM presented a significant association with tumor size ($p<0.001$), multifocality ($p<0.001$), lymph-adenectasis in lateral neck ($p<0.001$) and tumor extent ($p<0.001$). There were no significantly differences in age, gender, BRAFV600E mutation and subtype of PTC ($p>0.05$) (Table II). Multivariate analysis revealed that tumor size (OR: 2.07, 95% CI: 1.42 to 3.01, $p<0.001$), multimodality (OR: 2.67, 95%CI: 1.36 to 5.24, $p=0.004$), lymph-adenectasis in lateral neck (OR: 9.28, 95% CI: 3.73 to 23.12, $p<0.001$), tumor extent (OR: 4.97, 95% CI: 1.24 to 19.91, $p=0.024$) remained independent variables predictive of CLNM (Table III). Furthermore, comparisons were made between CLNM and tumor size, degree of tumor invasion, multifocal, location of solitary tumor. Dorsal part of solitary lesion (OR: 16.312, 95% CI: 3.349-79.455, $p=0.001$), capsular invasion (OR: 42.012, 95% CI: 5.209-338.861, $p<0.001$), $6<D\leq9$ (OR: 8.400, 95% CI: 1.866-37.807, $p=0.006$) and

Table II. Relationship of factors for CLNM.

Parameters	CLNM (+) n=80	CLNM (-) n=193	*p*-value
Age (year)			
< 45	48 (60)	118 (61.1)	0.861
≥45	32 (40.0)	75 (38.9)	
Gender			
Female	62 (77.5)	152 (78.8)	0.818
Male	18 (22.5)	41 (21.2)	
Tumor size (mm)			
$0<D\leq3$	28 (14.5)	2 (2.5)	<0.001*
$3<D\leq6$	82 (42.5)	21 (26.2)	
$6<D\leq9$	50 (25.9)	30 (37.5)	
D=10	33 (17.1)	27 (33.8)	
Multifocal			
Absent	30 (37.5)	132 (68.4)	<0.001*
Present	50 (62.5)	61 (31.6)	
Accompanying			
NG			
Absent	63 (78.8)	147 (76.2)	0.645
Present	50 (62.5)	46 (23.8)	
HT			
Absent	70 (87.5)	161 (83.4)	0.395
Present	10 (12.5)	32 (16.6)	
Lymphadenectasis of lateral neck			
Absent	53 (66.3)	184 (95.3)	<0.001*
Present	27 (33.8)	9 (4.7)	
BRAF[V600E]			
Negative	44 (55.0)	114 (59.1)	0.536
Positive	36 (45.0)	79 (40.9)	
Tumor extent			
Within capsule	62 (77.5)	191 (99.0)	<0.001*
Capsular invasion	16 (20.0)	1 (0.5)	
ECS	2 (2.5)	1 (0.5)	
Subtype			
Follicular variant	79 (98.8)	190 (98.4)	0.849
Ordinary	1 (1.2)	3 (1.6)	

*$p<0.05$ CLNM (+): central compartment LNM positive. CLNM (-): central compartment LNM negative. D: maximal diameter of lesion. NG: Nodular goiter. HT: Hashimoto's thyroiditis. ECS: extracapsular spread.

Table III. Multivariate logistic regression for central compartment LNM of PTM.

Variables	B	p-value	OR	95% CI of Exp
Age (year)	0.16	0.653	1.174	0.584-2.359
Gender	-0.183	0.673	0.832	0.355-1.952
Tumor size (mm)	0.728	<0.001*	2.071	1.424-3.010
Multifocal	0.938	0.004*	2.671	1.362-5.240
NG	0.135	0.748	1.145	0.502-2.614
HT	-0.203	0.679	0.816	0.312-2.135
Lymphadenectasis of lateral neck	2.228	<0.001*	9.28	3.726-23.12
BRAFV600E	0.179	0.616	1.196	0.595-2.404
Tumor extent	1.603	0.024*	4.968	1.240-19.91
Subtype	-2.092	0.432	0.123	0.001-22.67

*$p<0.05$ NG: Nodular goiter. HT: Hashimoto's thyroiditis. ECS: extracapsular spread.

D=1 (OR: 11.455, 95% CI: 2.500-52.480, $p=0.002$) were more tended to have CLNM. Results were showed in Table IV.

Transient and permanent hypocalcemia developed in 44 (26.4%) and 2 (1.2%), vocal fold palsy developed in 7(4.2%), 6 cases of vocal fold palsy recovered within six months (transient vocal fold palsy). One case of vocal fold palsy persisted for more than 1 year (permanent vocal fold palsy), and injection laryngoplasty was performed. Chyle leakage occurred in one patient, it was controlled nonoperatively with a fat-free diet.

Discussion

There is an increasing incidence of PTMC in Asia and all over the world through the improved methods and extensive use of diagnostic imaging[7,8]. Although PTMC has a good prognosis, the incidence of CLNM has been demonstrated in 30-60% and locoregional recurrence rates up to 20%[9,10]. Because of little prognostic benefit and postoperative transient hypocalcaemia, routine prophylactic CLND for PTMC has been debated[11-16]. Though some researches declared that

Table IV. Relationship of factors for CLNM.

Parameters	CLNM (+)	CLNM (-)	OR (95%CI)	p-value
Multifocal lesions				
In both lobes	29 (47.5)	32 (64.0)	1	
In one lobe	29 (47.5)	15 (30.0)	0.469 (0.210-1.044)	0.064
In isthmus and lobe	3 (4.9)	3 (6.0)	0.906 (0.169-4.850)	0.908
Solitary lesion				
Isthmus	2 (1.5)	2 (6.7)	4.643 (0.627-34.377)	0.133
Others	130 (98.5)	28 (93.3)	1	
Upper third	41 (31.5)	12 (42.9)	1	
Middle third	56 (43.1)	10 (35.7)	0.610 (0.241-1.548)	0.298
Lower third	33 (25.4)	6 (21.4)	0.621 (0.211-1.833)	0.388
Surface part	29 (22.3)	2 (7.1)	1	
Middle part	85 (65.4)	8 (28.6)	1.365 (0.274-6.799)	0.704
Dorsal part	16 (12.3)	18 (64.3)	16.312 (3.349-79.455)	0.001*
Tumor extent				
Within capsule	191 (99.0)	62 (77.5)	1	
Capsular invasion	1 (0.5)	16 (20.0)	42.012 (5.209-338.861)	<0.001*
ECS	1 (0.5)	2 (2.5)	3.507 (0.306-40.172)	0.313
Tumor size				
0<D≤3	28 (14.5)	2 (2.5)	1	
3<D≤6	82 (42.5)	21 (26.2)	3.585 (0.790-16.271)	0.098
6<D≤9	50 (25.9)	30 (37.5)	8.400 (1.866-37.807)	0.006*
D=1	33 (17.1)	27 (33.8)	11.455 (2.500-52.480)	0.002*

*$p<0.05$ CLNM (+): central compartment LNM positive. LNM (-): central compartment LNM negative. D: maximal diameter of lesion. ECS: extracapsular spread. ECS: extracapsular spread.

CLNM did not affect survival, more and more studies[17] reported regional LNM was in connection with increased local recurrence rates and reduced survival. The frequency of permanent complications was low in our work. With permanent hypocalcaemia in 1.2% and permanent vocal fold palsy in 0.6%. In previous studies, CLND did not increase permanent complications. Considering the low frequency of permanent complications, we suggest that prophylactic CLND is safe in experienced hands, but its prognostic benefit has not been proven. Therefore, it is really important to investigate the association between clinic pathologic factors and subclinical CLNM. As we known, the sex, size, multifocal and capsular invasion are all predictive factors for CLNM in patients with PTMC[18]. While in our work, we found no statistical correlations between age, gender, concomitant disease, BRAF V600E mutation, subtype of PTC and CLNM. Although 45-year-old is widely used as a clinical marker[19,20], researches studies reported that no association was found between age and LNM in patients with PTMC[21-23]. Our study shows that age is not predictive factor of CLNM. While male gender has previously been suggested as an indicator for LNM in previous investigations[20,24], the current paper showed that gender was not predictive of CLNM. There were few studies examined the effect of coexisting HT and NG with PTC on the LNM. Most of them reported negative results about the association between HT and CLNM[25]. Zhao et al[26] showed negative association between NG and CLNM. Also, we found no significant difference between HT, NG and CLNM. The association between clinic pathologic factors of PTC and BRAFV600E mutation has been extensively studied in the last decade[27]. However, it is still controversial now. BRAFV600E mutation has been reported to be correlated with multifocality, extrathyroidal extensive, LNM, and histological subtype in an advanced stage[28]. In contrast, others found no relationship between BRAFV600E mutation and CLNM[29] and our study demonstrated a negative result. Some previous works reported that subtype of PTC is not associated with CLNM in patients with PTMC[26,30], which was similar to our research. In the present investigation, we demonstrated that tumor size > 6 mm, multifocality, lymphadenectasis in lateral neck and capsular invasion, were independent predictors for CLNM of PTMC. Generally, CLNM is associated with a larger tumor size. Lim et al[21] demonstrated that tumor size, which was larger than 5 mm, had a stronger relationship with CLNM compared with less than 5 mm. Some researches[30,31] observed that PTMC with tumor size > 7 mm was frequently associated with poor prognosis. In this study, we have confirmed that tumor size > 6 mm was an independent predictor of CLNM by comparing four different diameters of PTMC. However, the association between multifocality and CLNM remains controversial. In this study, multifocality occurred in 40.7% of 273 PTMCs, and 62.5% of them had CLNM, which was similar to other studies[32,33]. In addition, multifocal PTC may grow from the clonal selection of a preneoplastic field, which may spread throughout the thyroid gland and result in CLNM[34]. By univariate and multivariate analysis, we showed that multifocal was an independent predictor of CLNM. However, there is no difference between bilateral multiple cancers, unilateral multiple cancer and isthmus with lateral lobe cancer. Specifically, by comparing different locations of solitary tumor, we found that dorsal part of solitary lesion is tended to have CLNM. Cervical lymph node metastasis occurs first to central compartment and subsequently to lateral neck. The skip metastasis to lateral neck in defect of CLNM is uncommon[35,36]. By comparing the preoperative lymph node status of lateral compartment and CLNM, lymphadenectasis in lateral neck was discovered as an independent risk factor for CLNM. Besides, lateral LNM was presented in 30 (83.3%) patients and 27 patients (90.0%) present both positive lateral LNM and positive CLNM. Capsular invasion is traditionally thought to be predictive for CLNM[18]. In this research, Capsular invasion was not rare (13.7%), which is consistent with the rate reported by previous studies (9.9-26.8%). Therefore, our research proved that, once again, Capsular invasion is an important prognostic characteristic of CLNM. Also, ECS is considered to be predictive for CLNM. However, in our study, we get an opposite result, it may contribute to adequate number of cases.

Conclusions

We showed that tumor size > 6 mm, multifocality, lymphadenectasis in lateral neck, capsular invasion are independent predictive factors for CLNM of PTMC. Prophylactic CLND may be recommended for these aggressive PTMC patients.

Conflict of Interest

The authors declared no conflict of interest.

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