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Original Article

Risk predictors for central lymph node metastasis and recurrence in CN0 papillary thyroid microcarcinoma

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Abstract: Surgical management of papillary thyroid microcarcinoma (PTMC), especially the need for central lymph node dissection, remains controversial. This study evaluated candidate risk factors of central lymph node metastasis (CLNM) to predict high-risk groups of CLNM from PTMC patients. Multivariate logistic regression analysis was used for 3,132 PTMC patients, who were surgically treated between 2005 and 2014, to determine the association of clinicopathologic factors and CLNM. A Cox regression model was used to determine the prognostic factors of recurrence. According to the results, CLNM was detected in 28.83% (903/3132) of the patients and 26.41% (956/3620) of the lesions. In multivariate analysis, males, age ≤ 35 years, with tumor size > 0.5 cm, lobe dissemination (+), psammoma body (+), capsular invasion (+), and multifocality were independent risk factors of CLNM. A nearly linear correlation was found between the CLNM rate and the tumor size in 10 groups ($y = 0.040x + 0.035$; $R^2 = 0.970$). A Cox regression model showed that tumor size > 0.5 cm, lobe dissemination (+), psammoma body (+), bilaterality (+), and CLNM were risk predictors of recurrence. In conclusion, due to the prevalence of CLNM in PTMC patients, we suggest that prophylactic CLN dissection could be performed routinely in CN0 PTMC patients, especially patients with the following factors: male, age ≤ 35 years, tumor size > 0.5 cm, lobe dissemination (+), psammoma body (+), capsular invasion (+), and multifocality, and more frequent follow-up should be considered for patients with tumor size > 0.5 cm, lobe dissemination (+), psammoma body (+), bilaterality (+), and CLNM.

Keywords: Thyroid cancer, microcarcinoma, regional metastasis, recurrence

Introduction

Papillary thyroid carcinoma (PTC) is the most common form of thyroid cancer, accounting for about 80% of all thyroid cancer cases [1, 2]. According to the World Health Organization, papillary thyroid carcinomas with diameters of ≤ 1.0 cm are diagnosed as papillary thyroid microcarcinomas (PTMC) [3]. Recently, in many regions of the world, the incidence of PTMC has been increasing rapidly and the clinical care of PTMC has become a management dilemma and a public health issue.

Although most of the PTMC cases are stable, without clinical symptoms, and may not endanger the patient's life, there are still some patients who have been found with neck lymph node metastasis or distant metastasis in the initial diagnosis [4]. The central compartment has been regarded as the most common compartment involved, and it is important for us to evaluate the status of the central lymph node (CLN) to determine the best operation method and improve the cure rate. Currently, more and more small nodules have been detected and diagnosed due to the advancement of ultrasonic equipment, but there are still certain limitations in evaluating CLNs by preoperative ultrasound. About 24%~64% of current PTMC patients have occult central lymph node metastasis (CLNM) according to some reports [5, 6].

Table 1. Patient demographics and clinical characteristics

Term	Case		Term	Case	
	Number	Percent		Number	Percent
Tumor size (cm)			Gender		
≤ 0.1	56	1.55%	Male	2457	78.45%
0.1~0.2	256	7.11%	Female	675	21.55%
0.2~0.3	492	13.66%	Caspsule invasion		
0.3~0.4	460	12.77%	Yes	2321	64.12%
0.4~0.5	628	17.43%	No	1299	35.88%
0.5~0.6	447	12.41%	Lobe dissemination		
0.6~0.7	359	9.97%	Yes	149	4.12%
0.7~0.8	354	9.83%	No	3471	95.88%
0.8~0.9		6.16%	Psammoma body		
0.9~1.0	346	9.61%	Yes	58	1.60%
Age (years)			No	3562	98.40%
≤ 25	81	2.59%	Bilaterality		
25~35	478	15.26%	Yes	976	26.96%
35~45	996	31.80%	No	2644	73.04%
45~55	1029	32.85%	Tumor number		
55~65	447	14.27%	1	2804	77.46%
> 65	101	3.22%	≥ 2	816	22.54%

There are no uniform professional guidelines for prophylactic CLN dissection, and it remains controversial as to whether or not prophylactic CLN dissection is needed for clinical lymph node negative (cN0) PTCM patients. The American Thyroid Association's (ATA) guidelines suggest that prophylactic CLN dissection can be considered for patients with advanced primary tumors (T3 or T4), which is equivocal to PTCM patients [7]. Thus, it is imperative for us to determine appropriate clinical and pathological predictors of CLNM to guide treatment decisions.

The aim of this retrospective study was to evaluate candidate risk factors of CLNM metastasis and to predict high-risk groups of CLNM from PTC patients. Data on the patients' prognoses were also gathered in order to identify risk factors of recurrence that may help to guide postoperative therapeutic decisions and follow-up for physicians and patients.

Material and methods

Patients and group

This retrospective study was approved by the Ethics Committee of Zhejiang Cancer Hospital, located in Hangzhou Zhejiang Province, China. It is a retrospective chart enrollment review of 3,132 patients who were first treated in the Department of Head and Neck Surgery, Zhejiang Cancer Hospital, between January 2005 and December 2014 due to the presence of PTC. All of the patients were pathologically diagnosed with PTMC. The patients with one or more of following conditions were excluded: 1) previous thyroid resection at another institution; 2) other types of thyroid malignancies; 3) a history of neck surgery for other diseases or radiation exposure; and 4) distant metastasis. Four hundred and eighty-eight patients with bilateral lesions were regarded as having 976 independent lesions, and a total of 3,620 lesions were included in the study. This cohort was then examined based on 8 clinical and histopathological characteristics: gender, age, tumor size, multifocality, lobe dissemination, psammoma body, capsular invasion, and bilaterality. Tumor size was based on the maximum diameter of the tumor. The number of tumors was based on preoperative ultrasonoscopy, and lesions were divided into a solitary group with only one nodule or a multifocality group with more than one nodule. Capsular invasion, lobe dissemination, and psammoma body were based on intraoperative frozen-section examination results and confirmed by paraffin-section post-operation.

Preoperative examination and surgery

All of the patients in the study underwent preoperative ultrasonography (US) examinations to determine the lymph node status and the number of tumors. The patients who met the following conditions could be diagnosed as cN0: 1) no palpable enlarged lymph node in the clinical examination or the maximum diameter of the enlarged lymph node was less than 2 cm with a soft texture; and 2) no visible enlarged lymph node in imaging examination, the maximum diameter of the enlarged lymph node was less than 1 cm, or the maximum diameter was 1~2 cm with no central liquefaction necrosis, peripheral enhancement, or missing fat gap adjacent to the lymph node [8]. Total thyroidectomy and bilateral CLN dissection was performed on the patients with bilateral PTC, while

Table 2. Correlation between clinico-pathologic factors and central lymph node metastasis

Term	Central lymph node metastasis				
	Negative	Positive	Case	Percent	*p* value
Gender					< 0.001
Female	1823	634	2457	25.80%	
Male	406	269	675	39.85%	
Age (years)					< 0.001
≤ 25	34	47	81	58.02%	< 0.001*
25~35	281	197	478	41.21%	
35~45	702	294	996	29.52%	
45~55	784	245	1029	23.81%	
55~65	344	103	447	23.04%	
> 65	84	17	101	16.83%	
Tumor size (cm)					< 0.001
≤ 0.1	51	5	56	8.93%	< 0.001**
0.1~0.2	225	31	256	12.11%	
0.2~0.3	418	74	492	15.04%	
0.3~0.4	376	84	460	18.26%	
0.4~0.5	500	128	628	20.38%	
0.5~0.6	304	143	447	31.99%	
0.6~0.7	244	115	359	32.03%	
0.7~0.8	217	137	354	38.70%	
0.8~0.9	136	86	222	38.74%	
0.9~1.0	193	153	346	44.22%	
Lobe dissemination					< 0.001
Yes	60	89	149	59.73%	
No	2604	867	3471	24.98%	
Psammoma body					< 0.001
Yes	20	38	58	65.52%	
No	2644	918	3562	25.77%	
Tumor number					< 0.001
Solitary	2118	686	2804	24.47%	
Multifocality	546	270	816	33.09%	
Bilaterality					0.815
Yes	721	255	976	26.13%	
No	1943	701	2644	26.51%	
Caspsule invasion					< 0.001
Absent	1821	500	2321	21.54%	
Present	843	456	1299	33.84%	

* age ≤ 35 years vs. age > 35 years, ** Φ ≤ 0.5 cm vs. Φ > 0.5 cm.

unilateral lobectomy plus isthmectomy and ipsilateral CLN dissection or total thyroidectomy and ipsilateral CLN dissection were performed on patients with unilateral PTC. According to the Chinese Thyroid Association's guidelines, total thyroidectomy might be considered when unilateral PTC patients met one of following conditions: 1) tumor size > 4 cm; 2) multifocal in one lobe; or 3) extrathyroid invasion.

Postoperative treatment and follow-up

All of the patients underwent conventional postoperative thyroid stimulating hormone (TSH) suppression therapy. Postoperative radioactive iodine (RAI) ablation therapy was performed in patients with total thyroidectomies and one or more of the following conditions: 1) T3 or T4; 2) positive lateral lymph node metastasis; or 3) distant metastasis. Patients underwent a conventional US examination every 3 months to detect local recurrence and computer tomography (CT) examination of the chest every year to detect lung metastasis. Every recurrence in the remnant thyroid gland or regional lymph nodes was diagnosed by US and confirmed by fine-needle aspiration or histological examination postoperation. Distant metastasis was diagnosed by CT and RAI scintigraphy after completion total thyroidectomy.

Statistics analysis

The Statistical Package for Social Science 18.0 (SPSS, Inc., Chicago, IL, USA) was used for statistical analysis. Univariate analysis was performed using Chi-square criterion and multivariate analysis was performed using logistic regression analysis. A Cox regression model was used to determine prognostic factors. A difference was considered to be statistically significant when two-sided p value < 0.05.

Results

Baseline characteristics

Among all of the patients, 28.83% (903/3132) and 26.41% (956/3620) of the lesions were detected to be histologically positive for central lymph node metastasis (CLNM). There were 675 males and 2457 females enrolled in the study, with the male/female ratio of 1:3.52, and the age ranged from 12-81 years, with a

Table 3. Multivariate logistic regression for Central Lymph Node Metastasis.

Variables	B	S.E	Sig.	Exp (B)	95.0% CI Exp (B)	
					Lower	Upper
Male	0.571	0.092	< 0.001	1.770	1.479	2.119
Age > 35 years	-0.718	0.099	< 0.001	0.488	0.401	0.592
Tumor size (Φ > 0.5 cm)	0.881	0.085	< 0.001	2.413	2.042	2.853
Lobe dissemination (+)	1.202	0.181	< 0.001	3.325	2.330	4.745
Psammoma body (+)	1.154	0.300	< 0.001	3.170	1.760	5.712
Caspsule invasion (+)	0.357	0.085	< 0.001	1.430	1.211	1.687
Bilaterality	-0.003	0.092	0.971	0.997	0.832	1.194
Multifocality	0.447	0.093	< 0.001	1.564	1.304	1.875

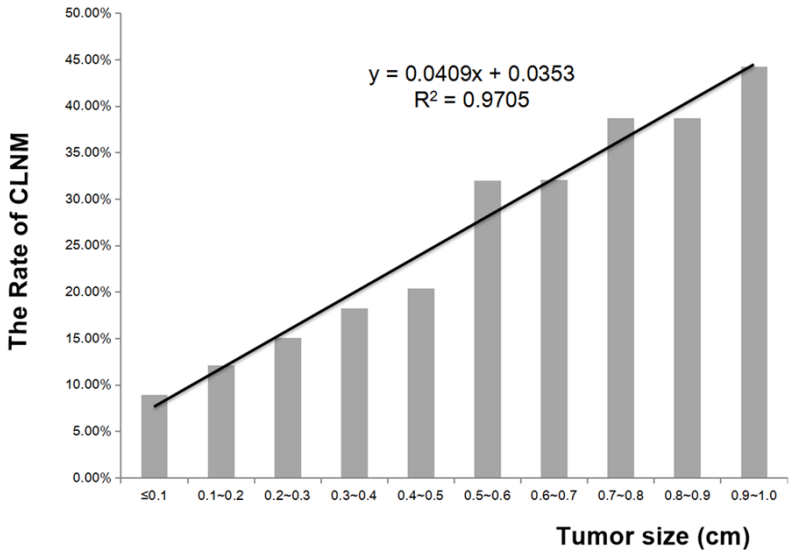

Figure 1. Tumor size is linearly related to the rate central lymph node metastasis in CN0 papillary thyroid microcarcinoma.

median age of 45.64 years. The diameter of the tumors ranged from 0.1-1.0 cm, with a median diameter of 0.551 cm. The median follow-up time was 43.0 months (with a range of 24.0-143.0 months) (**Table 1**).

Risk factors for CLNM

In our study, gender, age, tumor size, lobe dissemination, psammoma body, multifocality, and capsular invasion were found to be significantly associated with CLNM (P < 0.01) in the univariate analysis (**Table 2**). In the multivariate analysis, male (P < 0.001, odds ratio of 1.770), age ≤ 35 years (P < 0.001, odds ratio of 0.488), tumor size > 0.5 cm (P < 0.001, odds ratio of 2.413), lobe dissemination (+) (P < 0.001, odds ratio of 3.325), psammoma body (+) (P < 0.001, odds ratio of 3.170) capsular invasion (+) (P < 0.001, odds ratio of 1.430), and multifocality (P < 0.001, odds ratio of 1.508) were independent risk factors of CLNM, while no significant correlation was found between bilaterality and CLNM (**Table 3**).

In order to further evaluate the relationship between the tumor size and CLNM, patients were divided into 10 groups based on the maximum diameter of their tumors. According to the results, even in the group with tumor size ≤ 0.1 cm, there were still 8.93% of the patients who were found to be positive for CLNM. A significant difference in the CLNM rates was found between different groups, and the rate of CLNM increased obviously with the increase of tumor size. When the tumor size ≥ 0.5 cm, the CLNM rate increased to more than 30%. In addition, a nearly linear correlation was found between the CLNM rate and the tumor size in 10 groups ($y = 0.040x + 0.035$; $R^2 = 0.970$). In order to find a cutoff point for predictive CLNM, a Receiver Operating Characteristic (ROC) analysis was done, and the area under the curve was 0.654 (P < 0.01), indicating that Φ=0.5 cm could be considered the threshold to predict CLNM according to the curve (**Figure 1**).

The rate of CLNM increased with the decrease of age in a certain range, and a significant difference was found in the rate of CLNM between groups with different ages. In addition, the rate of CLNM was found to fluctuate widely between the group with 25 years < age ≤ 35 years and 35 years < age ≤ 45 years (41.21% vs. 29.52%), but became relatively stable when age ≥ 35 years, which indicated that perhaps age = 35

Table 4. Cox's Proportional Hazards Regression Model for Recurrence.

Variables	B	S.E	Sig.	Exp (B)	95.0% CI Exp (B)	
					Lower	Upper
Male	-0.063	0.309	0.838	0.939	0.512	1.721
Age > 35 years	0.077	0.335	0.817	1.080	0.561	2.081
Tumor size (Φ > 0.5 cm)	0.784	0.300	0.009	2.189	1.216	3.941
Lobe dissemination (+)	0.979	0.376	0.009	2.661	1.274	5.559
Psammoma body (+)	1.363	0.553	0.014	3.908	1.322	11.552
Caspsule invasion (+)	-0.234	0.247	0.344	0.792	0.488	1.285
Bilaterality (+)	1.228	0.289	< 0.001	3.413	1.936	6.017
Multifocality	0.240	0.291	0.408	1.272	0.720	2.248
CLNM	1.069	0.298	< 0.001	2.913	1.624	5.225

CLNM: Central Lymph Node Metastasis

years could be used as a cutoff point for predictive CLNM. Thus, we re-divided the patients and found that the CLNM rate was significantly higher in the group with age ≤ 35 years than in the group with age >35 years (P < 0.01) (**Table 2**).

Predictors of disease free survival (DFS) in patients with PTC

A total of 3,132 patients were followed up, with the median follow-up time of 43 months (with a range from 24-143 months). Fifty-seven patients (1.82%) were found with recurrence and 9 (0.28%) patients had died (only 4 (0.13%) were dead due to PTC). Thus, disease-free survival was chosen instead of overall survival due to the small number of patients who had died. The Cox regression model showed that tumor size > 0.5 cm (P = 0.009, hazard rate of 2.189), lobe dissemination (+) (P = 0.009, hazard rate of 2.661), psammoma body (+) (P = 0.014, hazard rate of 3.908), bilaterality (+) (P < 0.001, hazard rate of 3.413), and CLNM (P < 0.001, hazard rate of 2.913) were risk predictors of recurrence (**Table 4**). The DFS rate in patients with 4 or 5 risk predictors was significantly lower than in the other groups, which indicated that the patients with a larger number of risk predictors were usually more vulnerable to local recurrence (**Figure 2**).

Discussion

In recent decades, the incidence of thyroid cancer has increased rapidly across the globe, which, to some extent, can be attributed to the improvement of ultrasonic examinations. PTMC is one of the most common types of thyroid cancer and accounts for nearly 50% of new PTC cases [9]. The diagnosis of PTMC mainly depends on ultrasonography (US)–with the diagnostic accordance rate of high-resolution US ranging from 80.6%~81.5%–since the specificity and sensitivity of Computed Tomography (CT) and Magnetic Resonance Imaging (MRI)for tumors of less than 1 cm have not been satisfactory [10].

Despite the excellent prognosis of PTMC, some patients still experience cervical lymph node metastasis, especially CLNM. According to some reports, the central compartment (level VI) is the primary zone of lymphatic involvement in PTMC and the rate of CLNM ranges from 24%-64 % [11-13]. It was 28.83% in our study, which is in accord with previous studies. Presently, evaluation of CLNM mainly depended on US and contrast-enhanced CT, and the sensitivities of US and contrast-enhanced CT range from 23.0%-53.2% and 41.0%-66.7%, respectively [14-15]. The low sensitivity of US and CT may be due to several reasons. First, central metastatic lymph nodes are so small that they cannot be easily detected by US and CT. Second, it is difficult to evaluate posterior lymph nodes around the recurrent laryngeal nerve by US with the existence of an intact thyroid gland. Third, positive criteria for US and CT in the central neck have not yet been established [16]. Thus, CLNM is usually identified only when prophylactic central lymph node dissection has been performed.

There is no debate on CLN dissection for therapeutic purposes in PTMC patients, but the need for prophylactic CLN dissection is still an ongoing controversy because it seems to have little prognostic benefit [11, 17]. However, CLNM is an important risk factor of local recurrences and it is often missed by preoperative examinations [18]. Additionally, complete radical treatment of primary tumors with synchronous CLN dissection is not a complicated operation for experienced surgeons, and dissection can be done via the same incision as the thyroidectomy, but it is relatively difficult to re-operate on

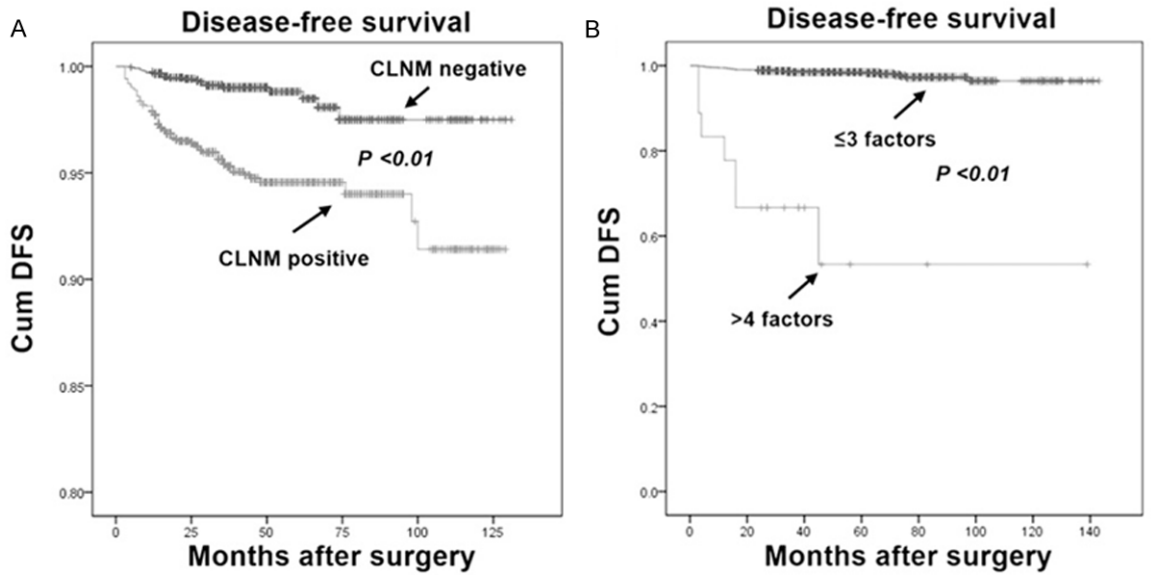

Figure 2. A. DFS rate in group with CLNM positive was significantly lower than group with CLNM negative (P < 0.01); B. DFS rate in groups with more than 3 predictive factors was significantly lower than other groups (P < 0.01).

patients with regional recurrence in the central compartment. Therefore, it has become increasingly crucial for us to investigate appropriate clinical and pathological factors associated with CLNM to guide treatment decisions.

Many studies have focused on the risk factors of central lymph node dissection (CLND) for CN0 patients, but the results are inconsistent. Mao et al. considered age ≤ 45 years and being male as independent risk factors of CLNM in PTC patients with a tumor size < 2.0 cm [19]. Sun W et al. [20] conducted a systematic review and meta-analysis of 9,084 patients and suggested that patients with age < 45 years, male, multifocality, tumor size > 2 cm for PTC patients or tumor size > 0.5 cm for PTMC patients, location of the primary tumor in the central area and lower pole, lymphovascular invasion, and extrathyroidal extension were more susceptible to CLNM. Our analyses of CLNM risk factors in patients with PTMC found that being male (P < 0.001, odds ratio of 1.770), age ≤ 35 years (P < 0.001, odds ratio of 0.488), tumor size > 0.5 cm (P < 0.001, odds ratio of 2.413), lobe dissemination (+) (P < 0.001, odds ratio of 3.325), psammoma body (+) (P < 0.001, odds ratio of 3.170) capsular invasion (+) (P < 0.001, odds ratio of 1.430), and multifocality (P < 0.001, odds ratio of 1.508) were independent risk factors of CLNM.

Tumor size is an important factor in the TNM staging system, and patients with larger tumor sizes were considered to be more susceptible to CLNM [21]. Some studies have suggested that tumor size = 0.5 cm should be a cutoff value for PTMC and tumor sizes ≤ 0.5 cm exhibited no micrometastases or contra-lateral CLNM in CN0 patients [22], but more detailed and profound studies evaluating the relationship between tumor size and CLNM have not been found. In this study, in order to make it clearer and unequivocal, we divided the patients into 10 groups based on the maximum diameter of the tumors, and we found a nearly linear correlation between the CLNM rate and tumor size in the 10 groups ($y = 0.040x + 0.035$; $R^2 = 0.970$), which indicated that the tumor size may be one of the most important influencing factors for CLNM. According to the results, even in the group with tumor sizes ≤ 0.1 cm, 8.93% of the patients were positive for CLNM, which reminded us that CLNM should not be ignored even in extremely small tumors. We also established a ROC curve and deduced that Φ=0.5 cm could be considered a threshold to predict CLNM. It is also important to note that patients with tumor sizes > 0.5 cm were more vulnerable to local recurrence.

It has been widely accepted that the incidence of PTC is higher in women, but men are inclined to higher rates of malignancy and mortality due

to PTC [23, 24]. In this study, being male was a risk factor for CLNM in PTMC patients, which suggested that males require specialized neck checkups to enable the early detection of thyroid tumors. However, no significant correlation was found between being male and recurrence.

Age is one of the most important factors in the TNM staging system, and the cutoff age of 45 years is widely used as a clinical marker for prognosis [25]. Patients with age > 45 years are more vulnerable to poor prognosis and local recurrence [26]. However, the role of age in CLNM still remains controversial. Lin DZ et al. considered that being age ≤ 45 years was significantly associated with a higher lymph node metastasis rate in PTMC patients. Particularly, children and adolescents (≤ 20 years of age) are more likely to have more advanced nodal stages at the time of diagnosis [27]. Our results showed that the rate of CLNM increased obviously with the decrease of age in a certain range and became relatively stable when age ≥ 35 years. Furthermore, we re-divided the patients and found that patients with age ≤ 35 years had an increased risk of CLNM than age > 35 years (43.65% vs. 25.6%, $P < 0.01$), which indicated that perhaps age=35 years could be used as a cutoff point for predictive CLNM.

Multifocality and capsular invasion have been found to increase the risk of local recurrence, as well as lymph node metastasis and distant metastasis [1, 28, 29]. An increasing number of tumors may be associated with more aggressive features and predicted poor prognosis in PTC [30]. Multifocality has also been proven to be related to lymph node metastasis and recurrence in PTC patients [31, 32]. Extrathyroidal extension exhibited a high propensity to spread to central lymph nodes in CN0 patients [19]. Xu DQ et al. [20] considered that patients with capsular invasion had an increased risk of CLNM in PTMC. The results of our study showed that multifocality and capsular invasion were independent predictive factors of CLNM.

Despite the good prognosis of PTMC, about 3.1~6.2% of patients underwent local recurrence [33, 34]. Mercante G et al. [35] suggested that capsular invasion, extrathyroidal tumor extension, and neck lymph node metastasis at presentation were the only independent risk factors for neck recurrence and/or distant metastasis occurrence. Pedrazzini L et al. considered that in PTMC patients without multifocality, extracapsular extension, or histologically proven lymph node metastases, lobectomy was associated with a very low risk of recurrence [36]. The data of our study shows that tumor size > 0.5 cm, lobe dissemination (+), psammoma body (+), bilaterality (+), and CLNM are risk predictors of recurrence. The DFS rate in patients with 4 or 5 risk predictors was significantly lower than in the other groups, which indicated that patients with a larger number of risk predictors were usually more vulnerable to local recurrence and more aggressive treatment, and more frequent follow-up should be considered for patients with 4 or 5 risk predictors.

In conclusion, our study identified the following risk factors for CLNM in CN0 PTMC patients: Male, Age ≤ 35 years, Tumor size > 0.5 cm, Lobe dissemination (+), Psammoma body (+), Caspsule invasion (+), Bilaterality (+), Multifocality. Besides, Tumor size > 0.5 cm, Lobe dissemination (+), Psammoma body (+), Bilaterality (+) and CLNM as risk predictors of recurrence in CN0 PTMC patients. Thus, due to the prevalence of CLNM in PTMC patients, we suggest that prophylactic CLN dissection could be performed routinely in CN0 PTMC patients, especially for the patients with risk factors mentioned above, and more frequent follow-up should be considered for patients with Tumor size > 0.5 cm, Lobe dissemination (+), Psammoma body (+), Bilaterality (+), and CLNM.

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Disclosure of conflict of interest

None.

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