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Original Article

Risk factors associated with lymph node metastasis in patients with small papillary thyroid carcinomas

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Abstract: Objective: This study aims to analyze risk factors for central lymph node metastasis (CLNM) in patients with small papillary thyroid carcinoma (PTC). Methods: The clinicopathologic data of 375 patients with small PTC admitted to the Affiliated Hospital of Inner Mongolia Medical University from January 2017 to December 2020 were analyzed retrospectively. The patients were divided into two groups, namely, CLNM (n = 177) and non-CLNM (n = 198) groups. Relevant data from the two groups were analyzed using the chi-square test, logistic regression analysis, and the receiver operating characteristic (ROC) curve. Results: The CLNM rate of the 375 patients with small PTC was 47.2%. The chi-square test revealed that CLNM status was correlated with a patient's gender and age as well as tumor size, number of lesions, and invasion of the thyroid capsule ($P < 0.05$), but not with BRAF gene mutation, Hashimoto's thyroiditis (HT), or nodular goiter. Multivariate analysis indicated significant differences in gender, maximum tumor diameter, multifocality, and thyroid adventitial infiltration between the two groups (all $P < 0.05$) but no significant difference between the two groups in regard to HT and nodular goiter. The ROC curve suggested that age ≤ 26.5 years and maximum tumor diameter ≥ 0.75 cm were thresholds for increased risk of CLNM. Conclusions: Lymph node metastasis in the central area of small PTC is associated with multiple factors. Careful examination, analysis, and evaluation of these factors can help in developing accurate individualized treatment strategies.

Keywords: Thyroid cancer, small papillary carcinoma, central lymph node metastasis, associated risk factors

Introduction

Over the past three decades, the incidence of thyroid cancer has markedly increased worldwide [1]. This increase is largely ascribable to an increase in the diagnosis of papillary thyroid cancer (PTC), especially small PTC. Small PTC refers to PTC with a diameter of less than 1 cm, usually with an occult onset and no obvious clinical symptoms, often accompanied by other benign thyroid diseases, such as Hashimoto's thyroiditis (HT), in 60%-70% of cases. It is often multicentric, with a high metastasis rate in the central region of the neck. It is usually detected by ultrasound imaging during incidental examination. Laboratory examination of small PTC usually displays no obvious abnormality, but when combined with HT, thyroid function abnormalities such as increased thyroglobulin and thyroid peroxidase may be present. Owing to the insidious onset, relatively slow course, and good prognosis of small PTC, its mortality rate is about 0.3% in the absence of invasive features. Therefore, patients with small PTC in the ultra-low risk group (T1aN0M0) can be followed up [2]. For patients with symptoms such as hoarseness caused by nerve invasion, cough caused by drinking water, or those with cervical lymph node metastasis, doctors mostly choose thyroid lobectomy or total thyroidectomy. Surgery is also preferred in case the disease imposes a heavy psychological burden on the patient and their family, capable of affecting their normal life and work [3]. Small PTC usually has a good prognosis, with a cure rate of 98%. However, once the patients with small PTC have cervical lymph node metastasis, the risk of recurrence, distant metastasis, and death tend to increase significantly [4]. Therefore, the study of risk factors for cervical lymph node metastasis of small PTC has a guiding role in the diagnosis and treatment of metastasis. Preoperative ultrasound examination and fine-needle aspiration biopsy (FNAB) have clear significance for

Table 1. Patients with different pathologic types of thyroid cancer n (%)

Total	Follicular thyroid carcinoma	Medullary thyroid carcinoma	Anaplastic thyroid carcinoma	Papillary thyroid carcinoma
2,758	132 (4.8)	78 (2.8)	24 (0.9)	2524 (91.5)

the discovery and diagnosis of small PTC. However, due to restrictions of the anatomic location and puncture technique, the positive rate of ultrasound for detecting lymph node metastasis in the central region of small PTC is not promising [5]. Ultrasound examination can indicate, for example, that the volume of lymph nodes has increased or the structure and morphology are abnormal, but the diagnosis of metastasis needs to be confirmed by approaches such as FNAB and intra/postoperative pathology. The overall rate of central lymph node metastasis (CLNM) was reported as 32%-48% [6, 7], all of which were confirmed by postoperative pathology. Our hospital is the largest clinical teaching center in Inner Mongolia, China, with an average diagnosis and treatment of over 700 cases of PTC every year, of which small PTC accounts for a large proportion. In this study, we analyzed risk factors for CLNM in patients with small PTC to provide a reference for treatment.

Materials and methods

General information

From January 2017 to December 2020, the Affiliated Hospital of Inner Mongolia Medical University admitted 2,758 patients with thyroid cancer and 2,565 patients with PTC (91.5%), including 375 patients with small PTC (13.6%) with complete data (**Table 1**). The data of those 375 patients were retrospectively analyzed. All patients underwent preoperative ultrasound examination of the thyroid and cervical lymph nodes, chest X-ray, and chest computed tomography (CT) examination, and some patients underwent a neck CT. All patients received frozen section pathologic examination during the operation and by postoperative routine pathologic examination. The patients were divided into a CLNM group (n = 177) and non-CLNM group (n = 198) according to the postoperative pathology. We used the patient's gender and age as well as maximum tumor diameter, tumor multifocality, whether the tumor invaded the capsule, and whether the tumor was complicated by HT or nodular goiter as evaluation criteria for the analysis of CLNM. The inclusion criteria were as follows: ① The first thyroidectomy and postoperative pathologic results were small PTC; ② Unilateral lobe and isthmus of the thyroid or total thyroidectomy plus central cervical lymph node dissection was performed; and ③ Clinicopathologic data were complete. The exclusion criteria were as follows: ① Previous history of malignant tumor; ② History of thyroid radiation exposure or previous surgery; ③ Pathologic diagnosis was non-small PTC; ④ Thyroid carcinoma with distant metastasis; ⑤ Patients underwent non-radical surgery; and ⑥ No follow-up examination in the first six months after the operation.

Surgical methods

All small PTC patients were routinely treated with unilateral or bilateral radical thyroidectomy (including central lymph node dissection). Lateral cervical lymph node dissection (LLND) was performed if lateral cervical lymph node enlargement was seen by preoperative ultrasound examination, or if lymph node metastasis was confirmed by FNAB.

Analysis of relevant data

The clinicopathologic data of the two groups were statistically analyzed, including patient's gender and age as well as maximum diameter of the tumor, tumor multifocality, whether the tumor had invaded the thyroid adventitia, and whether it was complicated by HT or with nodular goiter. The maximum tumor diameter was measured by pathologic examination. Multifocal thyroid tissue was defined as having two or more lesions from postoperative pathologic examinations. The presence or absence of HT and nodular goiter were confirmed by postoperative pathology. V-raf murine sarcoma viral oncogene homolog B1 (BRAF) gene was detected in 85 cases, while 79 cases were mutated, and the mutation rate was 92.9%. The correlation between BRAF gene mutation and CLNM was analyzed.

Table 2. Comparison of clinicopathologic features between two groups of patients with small papillary thyroid carcinoma, n (%)

Variable	Group	Cases	Transfer group (n = 177)	No transfer group (n = 198)	χ^2	*P*
Sex					11.708	0.001
	Male	61	41 (67.2)	20 (32.8)		
	Female	314	136 (43.3)	178 (56.7)		
Age (years)					8.208	0.017
	≤ 30	34	24 (70.6)	10 (29.4)		
	30 to	310	139 (44.8)	171 (55.2)		
	> 60	31	14 (45.2)	17 (54.8%)		
Tumor size (cm)					13.732	0.000
	≤ 0.5	182	68 (37.4)	114 (62.6)		
	> 0.5	193	109 (56.5)	84 (43.5)		
Multifocality					1.714	0.019
	Yes	150	77 (51.3)	73 (48.7)		
	No	225	100 (44.4)	125 (55.6)		
Invasion of thyroid adventitia					57.356	0.000
	Yes	106	83 (78.3)	23 (21.7)		
	No	269	94 (34.9)	175 (65.1)		
Hashimoto's thyroiditis (Cases)					0.385	0.535
	Yes	75	33 (44.0)	42 (56.0)		
	No	300	144 (48.0)	156 (52.0)		
Nodular goiter (Cases)						
	Yes	172	72 (41.9)	100 (58.1)	3.635	0.057
	No	203	105 (51.7)	98 (48.3)		

Follow-up

Among the 375 small PTC patients, 33 were lost to follow-up, leaving 342, with a follow-up rate of 91.2%. The patients were followed up until December 31, 2021, for 12-60 months. Postoperative lateral neck metastases were found in six patients (1.6%) without LLND. There were no cases of distant metastasis or death.

Statistical methods

SPSS26.0 statistical software was used to analyze the data. Enumerated data were expressed as percentages, and comparison between groups was performed by the chi-square test and Fisher's exact probability test. With the CLNM of small PTC as the variable factor (0, no; 1, yes), binary logistic regression analysis was used to analyze the associated risk factors. The receiver operating characteristic (ROC) curve was used to determine the cut-off values of age and maximum tumor diameter for predicting CLNM, at test level $\alpha = 0.05$.

Results

Clinicopathologic characteristics of the two groups

The respective relationships between CLNM and factors, namely, the patient's gender and age as well as maximum tumor diameter, tumor multifocality, whether it invaded the thyroid capsule, and whether it was complicated by HT or nodular goiter were analyzed and compared between the two groups (**Table 2**).

Multivariate analysis of CLNM

Patients' gender, age, maximum tumor diameter, multifocality, and invasion of the thyroid capsule were further included to construct a multivariate logistic regression equation. The results showed that the risk of CLNM was increased in men compared with women, and the difference was significant (OR = 2.476, 95% CI 1.267-4.840, P < 0.05). The risk of CLNM in small PTC patients with a maximum tumor

Table 3. Multivariate analysis of factors associated with central cervical lymph node metastasis in 375 patients with small papillary carcinoma

Variable	Group	Cases	OR	95% CI		*P*
				Lower	Upper	
Sex						
	Female	136	1.000			
	Male	41	2.476	1.267	4.840	0.008
Age (years)						0.425
	≤ 30	34	1.926	0.623	5.959	0.255
	30 to	310	1.093	0.489	2.444	0.828
	> 60	31	1.000			
Tumor size (cm)						0.000
	≤ 0.5	182	1.000			
	> 0.5	193	1.937	1.224	3.065	0.005
Multifocality	Yes	150	0.616	0.382	0.992	0.046
	No	225	1.000			
Invasion of thyroid adventitia	Yes	106	0.159	0.092	0.274	0.000
	No	269	1.000			

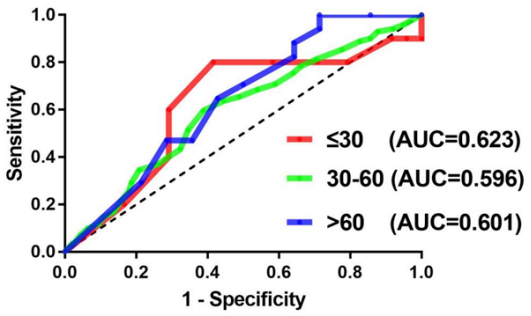

Figure 1. ROC curve analysis of age prediction of central lymph node metastasis (CLNM). ROC results showed that the cut-off value of age ≤ 30 years was 26.5 years, under which the sensitivity was 80.0%, the specificity was 58.0%, and the AUC was 0.623. The cut-off value of age between 30 and ≤ 60 was 45.5 years, under which the sensitivity was 59.7%, the specificity was 20.8%, and the AUC was 0.596. The cut-off value of age greater than 60 years was 69.5 years, under which the sensitivity was 100.0%, the specificity was 28.6%, and the AUC was 0.601.

diameter > 0.5 cm was higher than that of patients with a maximum tumor diameter ≤ 0.5 cm (OR = 1.936, 95% CI 1.224-3.065, P < 0.05). Multiple foci increased the risk of CLNM, and the difference was significant (OR = 0.616, 95% CI 0.382-0.992, P < 0.05). The influence of tumor lesions invading the thyroid capsule on lymph node metastasis was significant (OR = 0.159, 95% CI 0.092-0.274, P < 0.05; **Table 3**).

ROC curve of age and maximum tumor diameter in predicting CLNM

In this study, we noted that the younger the age, the higher the rate of CLNM. To further study the relationship between age and CLNM, an ROC curve was drawn for patients divided into three age groups: aged ≤ 30 years, 30-60 years, and > 60 years (**Figure 1**). By observing the ROC curve and comparing the area under the curve (AUC), we concluded that the influence of age ≤ 30 years on CLNM was higher than that for other age groups, with a cut-off value of 26.5 years, a sensitivity of 80.0%, and a specificity of 58.0% (**Figure 1**).

An ROC curve was further drawn to analyze the relationship between the maximum tumor diameter and CLNM divided into two groups of tumor sizes ≤ 0.5 cm and > 0.5 cm (**Figure 2**). By comparing the AUC of the curve, the impact of maximum tumor diameter > 0.5 cm on CLNM was greater than that of tumor diameter ≤ 0.5, the critical value was 0.75 cm, the sensitivity was 40.5%, the specificity was 75.2%, and the AUC was 0.5804, with P < 0.05.

Correlation analysis between BRAF gene mutation and CLNM

The CLNM rates of patients with and without BRAF gene mutation were 54.4% and 45.6%,

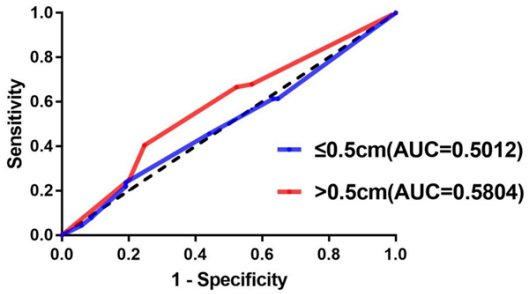

Figure 2. ROC curve analysis of maximum tumor diameter to predict CLNM. ROC results showed that the cut-off value was 0.75 cm when the maximum tumor diameter was more than 0.5 cm. Under this value, the sensitivity was 40.48%, the specificity was 75.23%, and the AUC was 0.5804. When the maximum tumor diameter was less than 0.5 cm, the cut-off value was 0.275 cm. Under this value, the sensitivity was 23.68%, the specificity was 80.88%, and the AUC was 0.5012.

respectively. No significant difference was found in the metastasis rate between the two groups (P = 0.741; **Table 4**).

Discussion

Small papillary thyroid carcinoma (PTC) refers to a PTC with a tumor diameter of less than 1 cm, which is difficult to detect. With the subcutaneous soft tissue of the neck, patients with small PTC often show no typical clinical features. Laboratory examinations have no practical significance for the diagnosis of small PTC either. For the diagnosis, it is reliable to use two-dimensional color Doppler ultrasound to diagnose factors such as volume, location, shape, boundary, presence of calcification, blood supply, aspect ratio, adjacent relationship with capsule and surrounding tissues, and whether there is cervical lymph node metastasis or distant metastasis. Furthermore, when it is difficult to distinguish between benign and malignant diseases with two-dimensional color Doppler ultrasound examination, then FNAB, molecular pathology diagnosis, CT, Magnetic Resonance Imaging (MRI), and positron emission tomography-CT (PET-CT) can be used to assist in diagnosis, since pathologic diagnosis is the gold standard in all examinations. At present, the treatment methods for small PTC are mainly surgical, minimally invasive treatment, and active surveillance.

All PTCs develop from small PTC, and the CLNM rate of small PTC has been reported to be 32%-48% [5, 6]. CLNM often develops into lateral neck lymph node metastasis and distant metastasis. Accurate assessment of CLNM and dissection of central and lateral neck lymph node metastasis can help curb the progression of the disease, reduce the risk of recurrence and metastasis, and avoid surgical complications. Preoperative ultrasonography can detect enlarged lymph nodes in the central region of small PTC. However, due to the limitations of anatomic site and puncture technique, the diagnosis rate is low, and it can only be confirmed by pathologic examination after intraoperative lymph node dissection. In this study, the risk factors for CLNM in small PTC patients were analyzed to evaluate the risk of CLNM in small PTC patients as early as possible. The rate of CLNM in this study was 47.2%, which was consistent with previous studies. We found that male gender with maximum tumor diameter ≥ 0.75 cm, multifocality, and capsular immersion were trisk factors for CLNM in small PTC. Whether the patients had HT and nodular goiter had no significant correlation with CLNM.

Most studies have found that the CLNM rate in male patients is significantly higher than that in female patients. Hence, being male is considered to be a risk factor for CLNM in cN0 small papillary carcinoma [7, 8], which is consistent with the conclusion of this study. However, some studies have reached the opposite conclusion [9, 10], which may be related to the small sample size, low proportion of male patients, study inclusion criteria, and differences in surgical methods. This study showed that the proportion of CLNM in small PTC patients aged ≤ 30 years was higher than that of other age groups. At present, it is generally believed that age < 45 years is a risk factor for CLNM in small PTC patients [11]. Oh et al. [12] divided 239 patients with cN0 small PTC into three age groups as age < 40, 40-50, and ≥ 50 years. The incidence of CLNM in each group was 86.9%, 46.6%, and 66.5% respectively, suggesting that age < 40 years was a risk factor for lymph node metastasis. In a prospective study, 1,235 small PTC patients were divided into three groups according to age < 40, 40-59, and ≥ 60 years, and similar conclusions were obtained [13]. Younger age is an independent risk factor for predicting the occurrence of CLNM in patients with small PTC, but there is no standard age cut-off point. In this study, 26.5 years was found to be the age cut-off

Table 4. Correlation analysis between gene mutation and central lymph node metastasis in 85 patients undergoing V-raf murine sarcoma viral oncogene homolog B1 (BRAF) gene testing n (%)

Variable	Total	Central lymph node metastasis	No central lymph node metastasis	χ^2	*P*
BRAF mutation	79	43 (54.4)	36 (45.6)	0.109	0.741
No BRAF mutation	17	10 (58.8)	7 (41.2)		

point for predicting the metastasis of central cervical lymph nodes of small PTC, which is relatively younger compared to the above studies. This may be attributed to the difference between the age groupings in this study and other studies. However, it can be generally deduced that the younger the age of patients with small PTC, the higher the likelihood of CLNM. It is well established that the larger the tumor size, the higher the risk of CLNM. Some scholars believe that the optimal critical value of CLNM for small PTC is 0.6 cm based on tumor diameter. Tumor diameter > 0.6 cm is significantly correlated with CLNM [14]. Further studies by Lee et al. [15] found that the occurrence of CLNM in small PTC patients was significantly correlated with tumor diameter > 0.7 cm. At present, most studies tend to take 0.7 cm as the cut-off value and confirm that a tumor diameter greater than 0.7 cm is the risk factor of CLNM in small PTC patients. In this study, we noted that maximum tumor diameter ≥ 0.75 cm was the critical value of CLNM in patients with small PTC, which was basically consistent with the above studies. However, prospective, large-sample studies are required to further determine the optimal cut-off value of tumor size for predicting CLNM in small PTC patients. Some scholars have found that multifocal tumor is a risk factor for CLNM in small PTC patients [16, 17], which is consistent with the conclusion of this study. At present, whether the multifocal origin of small PTC is intraglandular spread or independent occurrence has not been determined. In addition, intraglandular metastasis may occur through the rich lymphatic system between the glandular lobe and isthmus. This study shows that thyroid adventitial invasion is a risk factor for CLNM, which is consistent with previous studies [18, 19]. Clinical observation and follow-up are often adopted for small PTC patients with low-risk factors. As the tumor continues to grow, the scope of immersion is also expanded accordingly, which leads to a high proportion of adventitial immersion in surgical cases, and the proportion of lymph node tissue invasion along the adventitia is also increased.

Some studies have shown that the CLNM rate is lower in small papillary thyroid carcinoma patients with HT [12], but this study and other studies have shown that HT is not correlated with CLNM [8, 20]. This may be related to the small sample size and regional differences. A multicenter study with a larger sample size is needed to further evaluate the effect of HT on CLNM in small PTC patients. Clinically, many patients with small PTC combined with HT have more enlarged central cervical lymph nodes [21], but the metastasis rate is not high, so it is neither necessary nor appropriate to remove central lymph nodes. Recent studies have found that BRAF V600E mutation is the most common and critical genetic event in the progression of PTC. In addition, BRAF V600E mutation is only found in PTC and undifferentiated carcinoma derived from PTC and is not present in normal thyroid tissues, thyroid follicles, or other types of thyroid tumors [22]. Many studies have found that this mutation is associated with routinely known clinicopathologic features of PTC that predict tumor progression and recurrence, including advanced age, extrathyroidal invasion, lymph node metastasis, and advanced tumor stage. In addition, a direct association between BRAF V600E mutation and clinical progression, recurrence, and treatment failure of PTC has been demonstrated. At present, a few studies have investigated the link between BRAF V600E mutation and CLNM in small PTC. A meta-analysis showed that BRAF V600E mutation is an independent risk factor for CLNM in small PTC. However, because only five studies with 559 patients were included, and all of them were retrospective studies, the conclusion was not convincing [23]. In this study, a total of 85 out of 375 small PTC patients underwent BRAF gene testing, and 79 of them were found to have BRAF gene mutation, with a mutation rate of 93%. However, the sample size of BRAF gene test in this study was small. It is necessary to expand the sample size of BRAF gene test for further study to get a more accurate conclusion.

At present, the specific treatment of small papillary thyroid carcinoma is still controversial. A surgical approach is still the mainstay of treatment for small PTC, but the scope of excision is contentious. Currently, it is generally believed that the removal of affected side adenoidectomy plus isthmus resection and dissection of cervical lymph nodes should be recommended for small PTC patients with low-risk factors [24]. In this study, male gender, age ≤ 26.5 years, maximum tumor diameter ≥ 0.75 cm, multifocal tumor, and adventitial invasion were identified as risk factors for CLNM. Preventive central lymph node dissection should be performed when formulating surgical strategies. In recent years, thermal ablation has been gradually used in some low-risk small PTC patients and has achieved promising therapeutic effects [25]. Thermal ablation is regarded as a safe and effective treatment for low-risk small PTC patients who are unwilling to receive surgical treatment [25].

Active surveillance has been used in patients with small PTC for the past decade. Active surveillance as a treatment strategy for low-risk small PTC was first proposed in Japan, and the 2015 American Thyroid Association (ATA) guidelines included it as a management strategy for patients with low-risk small PTC [26]. The efficacy of this treatment in patients with low-risk small PTC largely depends on the accurate assessment of the patient's risk. Clinicians can take measures such as dynamic monitoring, risk stratification, and personal follow-up plans to reduce the risk.

Conclusions

In this study, CLNM was found to be correlated with gender, age, tumor size, tumor multifocality, and invasion of thyroid dorsalis. This study has a few shortcomings: the number of samples is relatively small. No statistical study was conducted on the relationship between CLNM and the general situation of patients, laboratory examination, or pathologic subtype of tumors. There are few studies on related susceptibility genes. Future studies can further refine the research indicators and include the pathologic subtypes of PTC and its gene expression as risk factor evaluation indicators. To get more accurate risk factor indicators, researchers must find other susceptible genes to provide more guidance for clinical treatment.

Disclosure of conflict of interest

None.

Abbreviations

CLNM, central lymph node metastasis; HT, Hashimoto's thyroiditis; PTC, papillary thyroid carcinoma; LLND, lateral cervical lymph node dissection; AS, Active surveillance; ATA, American Thyroid Association.

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