Original Article
Risk factors for predicting central lymph node metastasis in papillary thyroid microcarcinoma

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Abstract: Objectives: We aimed to determine the predictive factors for central compartment lymph node metastasis (LNM) in papillary thyroid microcarcinoma (PTMC). The outcome of the current study could assist greatly in decision-making regarding further treatment. Methods: Retrospective analysis of PTMC treated at the First Affiliated Hospital of Harbin Medical University. The predictive risk factors for central lymph node metastases (CLNM) were analyzed with respect to age, sex, tumor size, multifocal and capsular affection. Results: CLNM are common in thyroid microcarcinoma patients. The factors correlated with neoplasm size greater than 5 mm (odds ratio, 0.520; *P* = 0.001), tumor bilateral (odds ratio, 0.342; *P* = 0.020), and capsule invasion (odds ratio, 2.539; *P* = 0.000) were independently predictive of CLNM. In patients with a solitary primary tumor, tumor location in the lower third of the thyroid lobe was associated with a higher risk of CLNM. Conclusions: The risk factors such as male gender, tumor size > 5 mm, bilateral, multifocal location, lower third of the thyroid lobe and capsule invasion that can be identified preoperatively or intraoperatively, be considered for determination of prophylactic CLND in patients with PTMC.

Keywords: Papillary thyroid carcinoma, thyroid microcarcinoma, central lymph node, lymph node dissection, lymph node metastases

Introduction

Thyroid microcarcinoma (TMC) is defined as a malignant tumor measuring 1 cm or smaller in diameter [1]. With the advent of improved methods of diagnostic imaging such as computed tomography, magnetic resonance imaging and ultrasonography, the diagnosis of papillary thyroid microcarcinoma (PTMC) has been increased [2]. The treatment may vary from follow-up without surgery to a total thyroidectomy with or without radioactive iodine treatment. Although PTMC has an indolent course, the cervical lymph node metastasis (CLNM) of PTMC was reported in 12.3 to 64.1 per cent of patients and has been known to be associated with locoregional recurrence and distant metastasis [3, 4]. The role of central lymph node dissection (CLND) for PTMC has been debated because no evidence has demonstrated that CLND has better prognostic benefit. In addition, CLND can increase the frequency of postoperative transient hypocalcaemia. However, better knowledge about the risk factors for CLNM may guide clinical decisions regarding which cases require CLND. Therefore, we

investigated predictive factors for CLNM in PTMC using a large group of Chinese patients.

Materials and methods

Patients and surgical treatment

There were 939 patients with papillary thyroid carcinoma (PTC) initially treated at the Department of Thyroid and Breast Surgery, the First Affiliated Hospital of Harbin Medical University between January 2008 and January 2014; of these, 507 were diagnosed with PTMC histologically. During the first year of the study (2008~2009), PTMC accounted for 47% of PTC cases treated. However, during subsequent years, while the proportion of PTMC treated have progressively risen from 47% in 2008~2009 to 67% in 2013~2014, the total numbers of PTC patients has also varied over the years (**Figure 1**). These 507 patients represented 54% of the 939 patients with PTC (of all tumor sizes) who had their initial surgical therapy in our hospital over this time period. The characteristics of these patients are listed in **Table 1**.
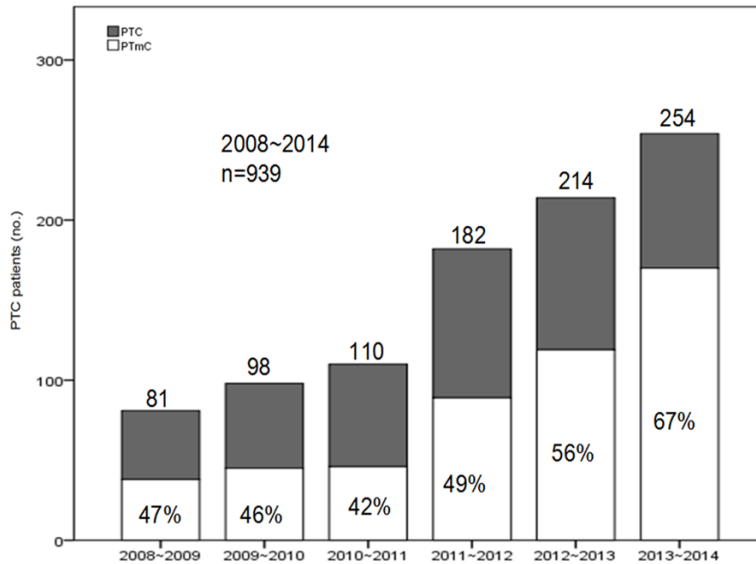
Figure 1. Frequency of PTM diagnoses during six years of the follow up. The numbers shown represent all PTC diagnosed during each year; percentages signify proportions of PTMC diagnosed during each year.

Table 1. Clinical and pathological characteristics of patients (n = 507)

	Number of patients (n)	Percent (%)
Gender		
Female	412	81.3
Male	95	18.7
Age at diagnosis (years)		
Mean	45.4 ± 11.2*	
< 45	234	46.2
≥ 45	273	53.8
Tumour size (mm)		
≤ 5 mm	261	51.5
> 5 mm	246	48.5
Bilaterality		
Yes	120	23.7
No	387	76.3
Multifocality		
Yes	147	29.0
No	360	71.0
Thyroid capsular invasion		
Yes	165	32.5
No	342	67.5
Diagnosis		
Incidental	398	78.5
Nonincidental (clinically suspected)	109	21.5

*Mean value ± standard deviation. CLNM, central lymph node metastasis.

The medical records of all patients with a final pathological report of PTMC were reviewed ret-

rospectively. Our database included age at the time of surgery, gender, surgical procedure performed, clinical characteristics and final pathology results, including bilaterality, multifocality, cervical lymph node involvement and capsule invasion. The location of the tumor within the gland was classified by which fourth of the thyroid lobe was involved (inferior, middle, superior, or isthmus). The association between primary tumor location and CLNM risk was analyzed using data from 305 patients with solitary primary lesions limited to one lobe. There were 110 patients with a primary lesion in the upper third of the thyroid lobe, 101 patients in the middle third, and 89 patients in the lower third (**Table 2**).

Diagnostic pre operative workup included: clinical examination, chest X-ray, neck and thyroid ultrasonography (US), elastography, and fine needle aspiration biopsy (FNAB). During the period of this study, we performed prophylactic CLND for patients without clinical metastatic nodes (cN0). The patients meeting the following conditions could be diagnosed as cN0: 1). No palpable enlarged lymph node in clinical examination or maximum diameter of enlarged lymph node was less than 2 cm with soft texture; 2). No visible enlarged lymph node in imaging examination or the maximum diameter of enlarged lymph node was less than 1 cm or the maximum diameter was 1~2 cm with no central liquefaction necrosis, peripheral enhancement or disappeared fat gap adjacent to lymph node. The histology of the frozen sections (FS) guided the extent of the surgical pro-

Table 2. Analysis of factors on cervical lymph node metastases in patients with PTMC (n = 402)

Variable	CLNM number (%)	Rate of metastasis (%)	P value
Gender			
Female	117 of 323 (36.2)	29.1	0.032
Male	39 of 79 (49.4)	9.7	
Age at diagnosis (years)			
< 45	83 of 192 (43.2)	20.6	0.082
≥ 45	73 of 210 (34.7)	18.2	
Tumour size (mm)			
≤ 5 mm	67 of 204 (32.8)	16.7	0.013
> 5 mm	89 of 198 (44.9)	22.1	
Location			
Bilateral	46 of 78 (58.8)	11.4	0.000
Ipsilateral	110 of 324(34.0)	27.4	
Tumor number			
Solitary lesion	103 of 305 (33.8)	25.6	0.000[a]
Upper third	26 of 110 (23.6)	6.5	0.028[b]
Middle third	41 of 101 (40.6)	10.2	
Lower third	35 of 89 (39.3)	8.7	
Isthmus	1 of 5 (20.0)	0.2	
Multifocal lesions	52 of 97 (53.6)	12.9	
Multifocal in both lobes	46 of 78 (59.0)	11.4	0.032[c]
Multifocal in affected lobe	6 of 19 (31.6)	1.5	
Thyroid capsular invasion			
Yes	57 of 119 (47.9)	14.2	0.015
No	99 of 283 (35.0)	24.6	
Chronic lymphocytic thyroiditis			
Absent	115 of 315 (36.5)	28.6	0.072
Present	41 of 87 (47.1)	10.2	

PTMC: papillary thyroid microcarcinoma. [a]The P value means the difference between the group solitary lesion and multifocal lesions. [b]The P value means the difference among the upper third, middle third, lower third, and isthmus in the group of solitary lesion. [c]The P value means the difference between the group multifocal in both lobes and in affected lobe in the group of multifocal lesions.

cedures. Lobectomy plus ipsilateral CLND was performed as the initial surgical treatment for PTMC patients with malignant lesions that were limited to a single lobe. When a benign or undetermined nodule was detected in the contralateral lobe by US, a subtotal lobectomy was performed in our hospital. When malignant lesions were found in both lobes of the thyroid by FS, a total thyroidectomy (TT) plus a bilateral CLND was performed.

Statistical analysis

Chi-square test and Fisher's exact test were used to analyze the significance of difference in the proportion of variables (univariate analysis).

Logistic regression analysis was performed for multivariate analysis to determine significant factors associated with CLNM. All statistical analyses were performed by using SPSS software (version 19.0; SPSS, Chicago). Values of P < 0.05 were considered statistically significant.

Results

Patient characteristics

Of 939 patients diagnosed with PTC, 402 (42.8%) cN0 patients with tumors sized 10 mm or less at the maximum diameter met the inclusion criteria. Of the 402 patients, 79 (16.65%) were men, 323 (83.35%) were women and the male/female ratio was 1/4.1 (**Table 2**).

The age of these 402 patients ranged from 16 to 78 years (mean 45.4 ± 11.2 years). Based on US and FS results, three different types of surgical procedures were performed: 1) lobectomy with ipsilateral CLND (121 patients); 2) lobectomy + ipsilateral CLND + subtotal lobectomy of the contralateral thyroid lobe (203 patients); 3) TT with a bilateral CLND (78 patients). Mean diameter of PTMC was 0.47 ± 0.17 cm (range, 0.1-1 cm). The characteristics of these 402 patients are listed in **Table 2**.

Clinicopathologic risk factors

Frequency of CLNM was greater in patients with multifocal neoplasm (P = 0.000), in patients whose tumor size greater than 5 mm (P = 0.000), and in patients with bilateral neoplasm (P = 0.000). Male patients and capsule invasion were also associated with CLNM (P = 0.032 and 0.015, respectively; **Table 2**). **Table 3** shows that there was an increased risk according to the location of the tumor when the

Table 3. The risk of location in the solitary primary tumor for CLNM adjusted for the factor of upper third

Variable	Adjusted OR	95% CI	P value
Location upper third	1		
Middle third	2.989	1.873~4.345	0.001
Lower third	13.047	8.587~20.787	0.001

Table 4. Multivariate analysis for risk factors of central lymph node metastasis

	P value*	Exp (β)ψ	95% CI. for Exp (β)	
			Lower	Upper
Gender (male)	.720	.913	.556	1.500
Size (> 5 cm)	.001	.520	.358	.755
Location (Bilateral)	.020	.342	.139	.845
Multifocal (present)	.820	.905	.381	2.150
Capsular invasion (present)	.000	2.539	1.729	3.729

*Logistic regression analysis. Exp (β)ψ: odds ratio for subclinical central lymph node metastasis. CI: confidence interval.

location was adjusted for the upper third, which indicates that patients with primary tumor in the lower third had a greater probability of suffering from CLNM than did those with a primary tumor in the upper third. Multivariate analysis showed that neoplasm size greater than 5 mm (odds ratio, 0.520; P = 0.001), tumor bilateral (odds ratio, 0.342; P = 0.020), and capsule invasion (odds ratio, 2.539; P = 0.000) were independently predictive of CLNM (**Table 4**).

Complications

Postoperative hypocalcaemia was defined as at least 1 event of hypocalcemic symptoms (perioral numbness, or paresthesia of hands and feet) or at least 1 event of biochemical hypocalcaemia (ionized Ca level < 1.0 mmol/L or total Ca level < 8.0 mg/dL). Among 402 patients, transient hypocalcaemia developed in 28 (6.97%) patients, and resolved within 6 months. Permanent hypocalcaemia developed in 3 patients (0.75%). Recurrent laryngeal nerve injury occurred in 5 patients (1.24%). 4 of these 5 cases was transient, and 1 of the 5 cases were permanent. Postoperative hematoma developed in 2 patients (0.50%) and was treated by reoperation.

Follow-up

All patients received TSH-suppressive hormonal therapy after surgery and thyroxine doses were adjusted to risk (to keep TSH below 0.1 mU/L for high-risk patients and from 0.1 to 0.3 mU/L for low-risk patients). Radioactive iodine therapy was not routinely prescribed for patients in this study because of its strictly controlled use in China. Radioactive iodine therapy was given following thyroxine withdrawal to selected patients with positive lymph nodes on pathology or who had distant metastasis. A routine periodic clinical examination (every 3 months in the initial year and then at yearly intervals) was mandatory, including neck ultrasound, whole body scans and serum TSH and basal thyroglobulin (Tg) levels with measurement of Tg antibodies.

Excluding 170 patients who were diagnosed with PTMC during 2013~2014, 232 patients adhered to a 12-month follow-up period, and many patients had a longer follow-up period. The mean length of follow-up was 28.5 months. The following criteria were used to define disease recurrence: either pathological evidence of disease on excision or cytology or recurrent disease confirmed by two surveillance modalities (e.g. elevated Tg and whole-body scan). During the follow-up period, there were no recurrences in central cervical compartment (level VI). Only 3 patients who underwent lobectomy with ipsilateral CLND (0.75%) suffered from a malignant recurrence in the contralateral lobe. This recurrence was resected; no patient demonstrated distant metastasis or died.

Discussion

The incidence of PTMC has been increasing in China and over the world with the advent of improved methods of diagnostic imaging. PTMCs account for nearly 50% of new cases of PTC [5]. Although the reasons for the rapid increase vary extensively, more and more studies have shown that papillary thyroid microcarcinomas (PTMC) account for a significant proportion of the increase [6]. An interesting finding of our study was that the proportion of PTMC treated have progressively risen from 47% in 2008~2009 to 67% in 2013~2014. The high incidence rate since 2012 may be attributed to the elastography for the evaluation of thyroid nodules. Presently, thyroid nodules are

often diagnosed in asymptomatic patients with many of these nodules frequently presenting as nonpalpable lesions. More than 60% of the population will present with thyroid nodules if screened with cervical ultrasonography. Elastography is a promising new technique that may improve the ultrasonic evaluation of thyroid nodules [7]. This technology evaluates tissue stiffness. Malignant lesions tend to be stiffer than the surrounding benign tissues. Elastography has been easily integrated into a routine ultrasound examination in our hospital since 2012.

Despite the overall prognosis of PTMC is general excellent, CLNM for some patients still exists. CLNM are usually identified only when prophylactic Level VI area lymph node dissection is performed. Wada et al. [8] reported that as high as 64% of all PTMCs had central node involvement after they followed a group of 259 patients, all of whom underwent lymph node dissection at the time of thyroidectomy. CLNM have previously been associated with tumor stage [9], increased risk of neoplastic progression [10], and were characterized as the most important prognostic factors for patients operated on for TMC [11, 12]. In our study, 156 patients had cervical lymph node metastases, representing 38.8% of all 402 patients. This percentage leads us to suggest that PTMC is not an indolent disease.

The opinion that patients with lymph node metastasis proved by physical examination or radiological findings must be performed lymphadenectomy has come to a consensus. Routine prophylactic CLND for PTMC has been debated because prophylactic CLND seems to have little prognostic benefit [13, 14]. CLNM, however, is an important risk factor of locoregional recurrences and often is not detected clinically. It is relatively difficult to reoperate on patients with regional recurrence in the central compartment. In addition, the central compartment can be dissected during thyroid surgery as it does not extend the wound. Therefore, investigation of the clinicopathologic factors associated with subclinical CLNM is of clinical importance. A variety of studies have been focused on the influencing factors of cervical lymph node metastases [15, 16]. Our analyses of influencing factors of cervical lymph node metastases in patients with TMC found that: The factors

correlated with neoplasm size greater than 5 mm (odds ratio, 0.520; P=0.001), tumor bilateral (odds ratio, 0.342; P = 0.020), and capsule invasion (odds ratio, 2.539; P = 0.000) were independently predictive of CLNM. In patients with a solitary primary tumor, tumor location in the lower third of the thyroid lobe was associated with a higher risk of CLNM. Patient age is known to be a significant prognostic factor, but in our study, age was not predictive of CLNM; frequency of subclinical CLNM was slightly greater in patients aged < 45 years. Previous studies suggested that the location of PTMC within the thyroid was related to the prevalence of CLNM [17, 18]. In our study of patients with a solitary primary tumor, we found that location in the lower third of thyroid lobe conferred a higher risk for CLNM. These results suggest that CLND may not be necessary for patients with only one tumor located in the upper third of the thyroid.

A meta-analysis on the safety of central lymph node dissection with total thyroidectomy for papillary thyroid carcinoma was performed by Pan Y et al. [19]. A total of 1524 patients were included, 620 were with total thyroidectomy plus central lymph node dissection and 904 with thyroidectomy alone. In their study, there was a significant increased risk of temporary hypocalcaemia and temporary vocal cord palsy when central lymph node dissection was performed in addition to a thyroidectomy. However, the risk of permanent hypocalcaemia and permanent vocal cord palsy has no statistical difference between the two groups. Recent studies of CLND report the development of permanent hypoparathyroidism in 0~4% of patients and the development of recurrent laryngeal nerve injury in 0~6% of patients, respectively; the temporary complication rates for these conditions were 47 and 5%, respectively [20, 21]. Hence, the advantage of prophylactic CLND should be weighed against the associated complications. In our study, permanent hypocalcaemia developed in 3 patients (0.75%). Recurrent laryngeal nerve injury occurred in 5 patients (1.24%). 4 of these 5 cases was transient, and 1 of the 5 cases were permanent. It suggests that routine CLND can be performed safely and with low morbidity by experts. Moreover, parathyroid autotransplantation was effective to reduce the complications related to parathyroid glands.

In our study, there were no recurrences in the central cervical compartment, which may results from effective removal of central LNM by CLND. We cannot, however, exclude the influence of short-term follow-up analysis in this study. This study does not address how to integrate ablative therapies such as radioiodine ablation into the treatment algorithm for patients with PTMC. Certainly, many centers have developed excellent local tumor control with such therapies. In our study, radioactive iodine therapy was not routinely prescribed for PTMC patients after surgery because of its strictly controlled use in China. Once the metastatic or recurrent lesions were detected, either surgical treatment or radioactive iodine therapy was suggested.

Conclusion

Taken together, though PTMC is generally associated with an excellent prognosis, patients may die of PTMC. The management of central lymph node is important in PTMC because recurrence of the central compartment can result in a serious problem such as invasion of the recurrent laryngeal nerve or trachea. Given these observations, it is hypothesized that a prophylactic CLND at the time of the original thyroidectomy would decrease the likelihood of cervical disease remaining. In addition, the risk factors such as male gender, tumor size > 5 mm, bilateral, multifocal location, lower third of the thyroid lobe and capsule invasion that can be identified preoperatively or intraoperatively, be considered for determination of prophylactic CLND in patients with PTMC.

Disclosure of conflict of interest

None.

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