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Original Article

The analysis of clinicopathologic predictors of lymph node metastasis and postoperative recurrence in patients with papillary thyroid microcarcinoma from Guangdong Province, China-a multicenter retrospective study

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Abstract: Purpose: Currently the extent of lymph node dissection (LND) for papillary thyroid microcarcinoma (PTMC) remains controversial. The present study aims to investigate the clinicopathologic predictors of lymph node metastasis (LNM) and prognosis in PTMC patients from Guangdong to enable appropriate treatment and follow-up. Methods: Data including demographics, tumor size, multifocality, extrathyroidal extension (ETE) and concomitant thyroiditis were collected from 374 untreated PTMC patients from Guangdong, China. Univariate and multivariate analyses were performed to identify clinicopathologic predictors of LNM and prognostic indicators in PTMC patients with LNM. Results: During the follow-up period of 120 months, recurrence was significantly higher in patients with LNM than in patients without LNM ($P<0.05$). Age <45 years, larger tumor (>5 mm) and multifocality were predictors of LNM; age <45 years, larger tumor size and absence of concomitant thyroiditis were associated with central LNM (CLNM); male sex, ETE and multifocality were correlated with lateral LNM (LLNM) ($P<0.05$). There was no difference in recurrence between patients with CLNM and LLNM ($P>0.05$). LNM in PTMC primarily influenced disease-free survival. Age >45 years and male sex were risk factors of recurrence in PTMC patients with LNM. Male patients with CLNM and older patients with LLNM exhibited worse prognosis ($P<0.05$). Conclusions: PTMC easily metastasizes to cervical lymph nodes, which significantly influences prognosis. Prophylactic LND is recommended in PTMC patients from Guangdong, China, who have a high risk of CLNM and/or LLNM. More aggressive postoperative treatment and more frequent follow-up could be considered for older and/or male PTMC patients with LNM.

Keywords: Papillary thyroid microcarcinoma, lymph node metastasis, clinicopathologic predictors, prophylactic lymph node dissection, prognosis, Guangdong province of China

Introduction

According to the World Health Organization classification system for thyroid tumors, papillary thyroid microcarcinoma (PTMC) is a papillary thyroid carcinoma (PTC) with a lesion measuring ≤10 mm in its longest diameter [1]. With improvements in ultrasound imaging and health awareness, the rate of detection of PTMC has significantly increased in Guangdong Province, China, according to the data from the Guangdong Center for Disease Control and Prevention. Although PTMC shows excellent overall prognosis based on long-term follow-up data, it is also associated with 1% disease-related mortality rate, 5% lymph node recurrence rate, and 2.5% distant metastasis rate [2]. Previous studies have revealed that the incidence of cervical lymph node metastasis (LNM) in PTMC is approximately 20 to 40%,

while the prevalence of subclinical central lymph node metastasis (CLNM) is 30-65% [3-5]. In addition, many studies have indicated that LNM in PTMC is one of the main predictors of recurrence and poor overall survival, and thus aggressive treatment, such as complete thyroidectomy combined with lymph node dissection (LND), radioactive iodine (RAI) ablation therapy, should be considered for patients with LNM [6].

Nevertheless, the therapeutic decisions of LNM in PTMC cannot be taken lightly because of potentially high prevalence and difficulty in the preoperative detection of LNM. Thus, the extent of LND in PTMC remains controversial. Some researchers agree that prophylactic LND enables better staging of disease that may guide subsequent treatment [7]; however, other studies insist that prophylactic LND should only be performed under certain circumstances [8]. The lack of consensus contributes to the indecision in surgeons regarding the treatment of PTMC patients with LNM. Unfortunately, both ultrasonography and contrast-enhanced computed tomography (CT) have low predictive accuracy for LNM, with sensitivities of 23%-53.2% and 41%-66.7%, respectively [9, 10]. Some studies have demonstrated that the risk factors of CLNM and LLNM are important for surgeons to determine the extent of neck LND [11]. However, the results of these studies are varied, and further investigation is therefore warranted.

This study aimed to investigate the clinicopathological predictors of LNM, including both CLNM and lateral lymph node metastasis (LLNM), in PTMC patients from Guangdong Province. The study also aimed to identify the prognostic factors that may predict postoperative recurrence/metastasis in PTMC patients with LNM, which might help guide appropriate treatment and follow-up plans to reduce the risk of recurrence and minimize overtreatment.

Materials and methods

Study design

This multicenter, retrospective study was performed in 4 hospitals in Guangdong, China, between July 1997 and July 2015. Preoperative ultrasonography was used to assess tumor size and LNM in patients. The patients received lobectomy or other types of thyroidectomy combined with the dissection of the central lymph node (level VI) and/or lateral lymph node (level II, III, IV and V) on the affected side based on the results of preoperative ultrasonography, intraoperative exploration and pathological assessment of frozen tissue sections. All operations were performed by senior surgeons from the general surgery department. In addition, diagnosis was confirmed via postoperative histopathology of paraffin sections. All patients were given thyroid-stimulating hormone (TSH) as suppression therapy throughout the follow-up period, and 66 patients received postoperative RAI therapy. During postoperative examinations, the level of thyroid hormones, TSH, thyroglobulin (TG) and anti-TG antibody was assessed. In addition, the patients were subjected to emission-computerized tomography (ECT), fine needle aspiration biopsy (FNAB) or neck ultrasonography once or twice per year for the detection of recurrence/metastasis. If recurrence/metastasis occurred, patients were given RAI therapy, and/or the recurrent/metastatic lesions were excised. Patients who presented with preoperative distant metastasis were excluded from the study. All clinical and follow-up data were collected from 4 medical centers in Guangdong Province to reduce selection bias and information bias. This retrospective study is fully compliant with the STROBE criteria.

Data collection

The collected data include demographics, surgical details, tumor status (tumor size, histopathological type, multifocality and extrathyroidal extension [ETE]), LNM, concomitant thyroiditis (chronic lymphocytic thyroiditis/Hashimoto's thyroiditis), postoperative complications (transient or permanent hypoparathyroidism, transient or permanent unilateral vocal cord palsy [VCP] and bilateral VCP) and recurrence/metastasis. Recurrence includes local recurrence of thyroid and/or regional lymph node and distant metastasis (such as lung, bone or multi-organ). In the case of multifocal PTMC, tumor size was calculated according to the diameter of the largest nodule.

Diagnostic criteria and statistical analyses

In this study, all diagnostic criteria were selected based on the 2016 NCCN guideline for thy-

Table 1. Clinicopathological characteristics of all enrolled patients

Variable	LN+* (%)	LN-* (%)	*P* value
Total	112 (29.95%)	262 (70.05%)	
Age			<0.001
<45	72 (64.29%)	100 (38.17%)	
≥45	40 (35.71%)	162 (61.83%)	
Sex			<0.001
Male	42 (37.50%)	46 (17.56%)	
Female	70 (62.50%)	216 (82.44%)	
Tumor size			<0.001
≤0.5 cm	42 (37.50%)	164 (62.60%)	
>0.5 cm	70 (62.50%)	98 (37.40%)	
Tumor location			0.001
Unilateral lesion	68 (60.71%)	206 (78.63%)	
Bilateral lesion	44 (39.29%)	56 (21.37%)	
ETE*			0.031
Yes	10 (8.93%)	8 (3.05%)	
No	102 (91.07%)	254 (96.95%)	
Concomitant thyroiditis			0.002
Absent	107 (95.54%)	220 (83.97%)	
Present	5 (4.46%)	42 (16.03%)	
Multifocality			<0.001
Monocentric lesion	54 (48.21%)	190 (72.52%)	
Multicentric lesion	58 (51.79%)	72 (27.48%)	
Local recurrence	20 (17.86%)	14 (5.34%)	<0.001
Distant metastases	3 (2.68%)	0 (0%)	
Postoperative complications			
Total	4 (3.57%)	3 (1.15%)	0.111
Unilateral VCP*	2 (1.79%)	1 (0.38%)	
Bilateral VCP*	0 (0%)	0 (0%)	
Temporary hypoparathyroidism	2 (1.79%)	2 (0.76%)	
Permanent hypoparathyroidism	0 (0%)	0 (0%)	

*LN+: patients with lymph mode metastasis; LN-: patients without lymph node metastasis; ETE: extrathyroidal extension; VCP: vocal cord palsy.

roid carcinoma. Tissue slides were reviewed by two senior pathologists. The indications for postoperative RAI therapy included LNM, ETE and multifocal disease, etc. [12] Recurrence and metastasis were definitively diagnosed based on pathology (using biopsy or resection) or considered highly likely in the case of suspicious imaging and supporting serologic results.

Statistical analyses were performed with SPSS 20.0 (SPSS, Inc., Chicago, IL, USA). All qualitative data were expressed as percentage and analyzed using Pearson's chi-square test or Fisher's exact test. The risk factors for LNM and recurrence were analyzed by univariate and multivariate analysis using binary logistic regression. The statistical significance level for all tests was set at $P<0.05$ (two-tailed tests).

Results

Patient characteristics

During the median follow-up period of 120 months (ranging from 60 to 228 months), 374 PTMC patients consisting of 88 males and 286 females were enrolled in our study. Among the 374 patients who underwent LND, 147 had only the central lymph nodes removed, 154 had only the lateral lymph nodes removed, and 73 had both central and lateral lymph nodes removed. Patients were divided into two groups according to LNM. Group A had 112 patients (29.95%) with LNM, and group B had 262 patients (70.05%) without LNM. None of the patients died during follow-up. Patient characteristics are given in **Table 1**. The proportion of patients with younger age (<45 years), male sex, larger tumor size (>5 mm), bilateral tumor location, ETE and multifocality was significantly higher in group A than that in group B, whereas the proportion of patients with concomitant thyroiditis showed the opposite trend ($P<0.05$). In addition, the rate of postoperative recurrence and metastasis was significantly higher in group A (17.86% and 2.68%, respectively) than that in group B (5.34% and 0%, respectively). There was no difference in postoperative complications between the groups ($P=0.111$).

Clinicopathological risk factors of CLNM

Forty-two patients (11.23%) had CLNM. In univariate analysis, younger age, larger tumor size and absence of concomitant thyroiditis in patients were significantly associated with an

Table 2. Univariate analysis of predictive factors of LNM in PTMC

Predictive factors	CLNM*			LLNM*			Any LNM*		
	OR*	CI*	*P* value	OR*	CI*	*P* value	OR*	CI*	*P* value
Age	0.470	0.225-0.981	0.044	0.706	0.375-1.329	0.281	0.509	0.301-0.861	0.012
Sex	1.548	0.675-3.550	0.303	3.170	1.665-6.037	<0.001	1.927	1.092-3.400	0.024
Tumor size	2.468	1.187-5.133	0.016	1.516	0.816-2.816	0.188	2.169	1.299-3.621	0.003
Tumor location	1. 591	0.443-5.715	0.477	2.165	0.803-5.833	0.127	2.101	0.853-5.178	0.107
ETE*	0.862	0.256-2.898	0.810	4.365	1.518-12.548	0.006	0.390	0.148-1.028	0.057
Multifocality	1.603	0.491-5.230	0.434	3.683	1.498-9.053	0.004	3.080	1.351-7.023	0.007
Concomitant thyroiditis	0.425	0.197-0.917	0.031	0.618	0.343-1.113	0.109	1.002	0.605-1.657	0.995

*CLNM: central lymph node metastasis; LLNM: lateral lymph node metastasis; LNM: lymph node metastasis; ETE: extrathyroidal extension; OR: odds ratio; CI: confidence interval.

Table 3. Multivariate analysis of predictive factors of LNM in PTMC

Predictive factors	CLNM*			LLNM*			Any LNM*		
	OR*	CI*	*P* value	OR*	CI*	*P* value	OR*	CI*	*P* value
Age	0.449	0.225-0.896	0.023	--	--	--	0.486	0.294-0.804	0.005
Sex	--	--	--	3.387	1.885-6.089	<0.001	1.669	0.962-2.896	0.069
Tumor size	2.338	1.168-4.682	0.017	--	--	--	2.065	1.271-3.355	0.003
ETE*	--	--	--	5.311	1.905-14.812	0.001	--	--	--
Multifocality	--	--	--	2.167	1.219-3.853	0.008	2.003	1.223-3.281	0.006
Concomitant thyroiditis	0.436	0.203-0.934	0.033	--	--	--	--	--	--

*CLNM: central lymph node metastasis; LLNM: lateral lymph node metastasis; LNM: lymph node metastasis; ETE: extrathyroidal extension; OR: odds ratio; CI: confidence interval.

Table 4. Comparison of prognosis between PTMC patients with different types of LNM

	CLNM*	LLNM*	*P* value
Local recurrence	7 (16.67%)	13 (18.57%)	0.799
Distant metastasis	1 (2.38%)	2 (2.86%)	0.880

*CLNM: central lymph node metastasis; LLNM: lateral lymph node metastasis.

increased risk of CLNM ($P<0.05$), whereas sex, tumor location, ETE and multifocality were not ($P>0.05$, **Table 2**). In multivariate analysis, younger age (OR=0.449 [OR=odds ratio], CI=0.225-0.896 [CI=Confidence interval]), larger tumor size (OR=2.338, CI=1.168-4.682) and absence of concomitant thyroiditis (OR=0.436, CI= 0.203-0.934) were independent predictors for high prevalence of CLNM (**Table 3**).

Clinicopathological risk factors of LLNM

Among the 374 patients, 70 (18.72%) had LLNM. In univariate analysis, male sex, ETE and multifocality were significantly associated with an increased risk of LLNM ($P<0.05$), whereas age, tumor size, tumor location and absence of concomitant thyroiditis were not ($P>0.05$, **Table 2**). In multivariate analysis, male sex (OR=3.387, CI=1.885-6.089), ETE (OR=5.311, CI=1.905-14.812) and multifocality (OR=2.167, CI=1.219-3.853) were found to be associated with a high risk of LLNM ($P<0.05$, **Table 3**).

Clinicopathological risk factors of LNM

Univariate and multivariate analyses were conducted in all 374 patients to determine the predictive factors of LNM in PTMC. The results of univariate analysis showed that age <45 years, male sex, primary tumor diameter >5 mm and multifocality were risk factors for LNM ($P<0.05$, **Table 2**). The results of multivariate analysis of predictive factors for LNM are illustrated in **Table 3**. Younger age (OR=0.486, CI=0.294-0.804), larger tumor size (OR=2.065, CI=1.271-3.355) and multifocality (OR=2.003, CI=1.223-3.281) were identified as the main factors influencing LNM in PTMC ($P<0.05$). However, male sex was not validated as a significant risk factor for LNM in multivariate analysis ($P=0.069$).

Comparison of prognosis between CLNM and LLNM

The incidence of recurrence and metastasis between patients with CLNM and LLNM is illus-

Table 5. Univariate analysis of prognostic factors of postoperative recurrence/metastases in PTMC with LNM

Predictive factors	Central LNM*			Lateral LNM*			Any LNM*		
	OR*	CI*	*P* value	OR*	CI*	*P* value	OR*	CI*	*P* value
Age	0.172	0.014-2.073	0.166	7.165	1.895-27.088	0.004	3.846	1.359-10.889	0.011
Sex	7.916	2.882-71.065	0.015	2.020	0.586-6.965	0.266	5.018	1.848-13.626	0.002
Tumor size	6.200	0.523-73.541	0.148	2.255	0.589-8.634	0.235	1.912	0.680-5.380	0.219
Tumor location	0.083	0.002-3.094	0.178	4.529	0.721-28.454	0.107	1.255	0.318-4.945	0.746
ETE*	0.0007	--	0.998	3.627	0.464-28.328	0.219	1.263	0.292-5.467	0.755
Multifocality	1.645	0.081-33.523	0.746	2.447	0.465-12.872	0.291	1.592	0.409-6.205	0.503
Concomitant thyroiditis	3.594	0.397-32.519	0.255	0.531	0.166-1.698	0.286	1.049	0.441-2.491	0.915

*CLNM: central lymph node metastasis; LLNM: lateral lymph node metastasis; LNM: lymph node metastasis; ETE: extrathyroidal extension; OR: odds ratio; CI: confidence interval.

Table 6. Multivariate analysis of prognostic factors of postoperative recurrence/metastases in PTMC with LNM

Predictive factors	Any LNM*		
	OR*	CI*	*P* value
Age	2.848	1.160-6.994	0.022
Sex	4.123	1.695-10.027	0.002

*LNM: lymph node metastasis; OR: odds ratio; CI: confidence interval.

trated in **Table 4**. Although local recurrence and distant metastasis was higher in patients with LLNM than that in patients with CLNM, there was no significant difference in local recurrence and distant metastasis between patients with CLNM and LLNM (*P*=0.799 and 0.880, respectively), indicating that the type of LNM does not impact the prognosis of PTMC patients from Guangdong Province. Moreover, because none of the patients died of PTMC during the follow-up period, it is likely that LNM primarily influences disease-free survival (DFS) rather than overall survival (OS) in PTMC patients from this region.

Prognostic factors of postoperative recurrence/metastasis in PTMC patients with LNM

During the median follow-up period of 120 months, 23 patients among the 112 PTMC patients with LNM experienced recurrence/metastasis. Male patients with CLNM exhibited significantly worse prognosis than female patients with CLNM (OR=7.916), and older age was a significant predictor of poor prognosis in PTMC patients with LLNM (OR=7.165, **Table 5**). In addition, older age (OR=2.848, CI=1.160-6.994) and male sex (OR=4.123, CI=1.695-10.027) were determined to be significant risk factors for local recurrence/distant metastasis in both univariate and multivariate analyses in PTMC patients with LNM from Guangdong Province (*P*<0.05, **Tables 5** and **6**). Other factors, such as tumor size, tumor location, ETE, multifocality and absence of concomitant thyroiditis were not associated with recurrence in PTMC patients with LNM (**Table 5**).

Discussion

With improvements in ultrasonography techniques and an increase in health awareness among individuals, the detection rate of PTMC has significantly increased. PTMC accounts for 21.7%-49.0% of all thyroid cancers [13]. It is generally considered an indolent disease due to its low recurrence rate and high OS, but postoperative recurrence, metastases and disease-related mortality are still common in patients with PTMC [14]. Some studies have reported that the rate of LNM in PTMC is approximately 20%-40% [3-5]. In this study, we found that 29.95% of all enrolled patients undergoing LND had LNM. Although the mortality due to PTMC does not substantially increase in the presence of LNM, the risk of postoperative recurrence/metastases significantly increases [15]. In our study, the postoperative recurrence/metastasis rate was significantly higher in patients with LNM (20.54%) than that in patients without LNM (5.34%), which is consistent with findings reported in the literature.

The significance of routine prophylactic LND in PTMC remains controversial, and whether this procedure increases OS or decrease recurrence remains unclear. A recent study has shown that prophylactic LND does not increase the incidence of postoperative complications

such as hemorrhage, permanent hypoparathyroidism or permanent recurrent laryngeal nerve injury, but the lack of prophylactic LND significantly increases the risk of recurrence [16]. To some extent, these discrepancies are often due to the inadequate estimation of risk factors of LNM in PTMC [1]. Therefore, it is important to explore the clinicopathological risk factors of LNM in PTMC to aid in the appropriate regional LND in patients from Guangdong Province who belong to a selective high-risk population.

In this study, multivariate logistic analyses were used to investigate the clinicopathologic factors predicting LNM. The previously identified predictors of LNM in PTMC are age, gender, tumor size, tumor multifocality and ETE [17]. In the PTMC patient population from Guangdong Province, China, we determined that younger age (<45 years), larger tumor size (>5 mm) and absence of concomitant thyroiditis were significantly associated with CLNM, while male sex, ETE and multifocality were significantly associated with LLNM. In addition, younger age, larger tumor size and multifocality were the main factors influencing LNM. According to a previous study, the age of patients at first admission is correlated with LNM in PTMC, whereby younger patients are more likely to have a higher incidence of LNM [18]. However, some studies have demonstrated the lack of difference in the risk of LNM between patients <45 years and ≥45 years of age [19]. In contrast, Kim et al. have reported an inverse relationship between age and LNM [20]. Our results also indicated that younger age was associated with a higher risk of LNM in PTMC patients from Guangdong Province. In addition, tumor size is another important predictor to LNM in PTMC. Several studies have reported that patients with a tumor size >5 mm had a higher risk of LNM [18, 21], which is consistent with our results. However, the correlation between concomitant thyroiditis and LNM in PTMC has been debated. The rate of concomitant chronic lymphocytic thyroiditis with PTMC has been reported to range from 10% to 58% [22]. Some investigators have reported that PTMC patients with chronic lymphocytic thyroiditis have good prognosis because of the low incidence of nodal and distant metastasis [23]. Kim et al. have reported a negative association between concomitant chronic lymphocytic thyroiditis and CLNM in PTMC patients [24]. Our results also indicated that concomitant thyroiditis in PTMC patients is negatively correlated with CLNM ($P<0.05$). This relationship may be due to the different pathological and physiological features of the two diseases. Furthermore, previous studies have indicated that the rate of LNM in PTMC patients with multifocal lesions is approximately 55.6% in comparison with 28.6% in patients with unifocal disease [3]. Lombardi et al. studied 933 patients with PTMC and found that the risk for cervical nodal recurrence increased by 17.9-fold in the presence of multifocal disease at the time of diagnosis [25]. However, some studies have reported different conclusions [26]. We found that 51.79% of patients with multifocal lesions had LNM, and both univariate and multivariate analyses showed that tumor multifocality was associated with LNM (OR=2.003, $P=0.006$). This may be due to the increase in invasiveness of multifocal tumors.

Furthermore, according to previous studies, larger tumor size, ETE and younger age are associated with higher rate of CLNM [1], consistent with our results. Although the risk of LLNM in PTMC has not been well studied yet, one study demonstrated that PTMC patients with ETE (OR=7.925), multifocal tumors (OR=3.560) and CLNM (OR=2.334) were significantly more likely to have LLNM [27], similar to our findings. In addition, another study identified male sex as a risk factor for LLNM, suggesting that males require careful examination of the thyroid to enable the early detection of PTMC [18]. However, the male sex was not identified as an independent predictor of CLNM and LNM by multivariate analysis in our study. The heterogeneity of LNM may be due to differences in patients, sampling error and subtle variations in surgical procedures among different surgeons.

Although PTMC has a high propensity of nodal metastasis, and LNM is a prognostic indicator of PTMC, according to the current guidelines, prophylactic LND is generally not recommended for patients with clinically node-negative (cN0) [28]. However, considering that subclinical LNM is unlikely to be eradicated by RAI therapy, leading to subsequent regional recurrence, [29] and that scarring due to reoperation may increase the risk of recurrent injury to the laryngeal nerve and parathyroid tissues, some studies have indicated that removal of occult nodes in the central compartment may confirm the status of involvement of the central lymph node

and help in predicting LLNM and guiding treatment [30]. Thus, from the perspective of radical treatment of tumors, prophylactic central LND should be considered in PTMC patients from Guangdong Province who are younger and have larger tumors in the absence of concomitant thyroiditis at the time of initial operation to reduce tumor persistence. Nevertheless, the rationale for prophylactic lateral LND in PTMC is also controversial. Currently, there is no effective preoperative examination to confirm the existence of LLNM. Some researchers conducted prospective quantitative evaluation of LLNM in PTMC without clinical LLNM and found that the incidence of occult LLNM was as high as 55% and that LLNM had negative impact on prognosis [31]. Our results revealed that 11.23% of patients had CLNM and that 18.72% patients had LLNM, and patients with LLNM had higher postoperative recurrence rate (21.43%) than patients with CLNM (19.05%). Therefore, central LND alone may not be enough for certain PTMC patients, and prophylactic lateral LND may be recommended in high-risk PTMC patients from Guangdong Province, such as male patients with ETE and multicentric lesions.

Although the incidence of local recurrence and distant metastasis was higher in patients with LLNM (18.57%, 2.86%) than in patients with CLNM (16.67%, 2.38%), there was no significant difference in local recurrence/distant metastasis between patients with CLNM and LLNM (P=0.799 and 0.880, respectively). Thus, the type of LNM does not affect the postoperative prognosis of PTMC patients from Guangdong. In addition, because none of the patients died of PTMC during the follow-up period, it is likely that LNM primarily influences DFS rather than OS of PTMC patients from Guangdong, which is consistent with the findings of a previous study [15]. Therefore, both CLNM and LLNM can potentially result in a high recurrence rate and thus should be treated radically for certain high-risk patients from this region.

Despite the extent of recurrence in different types of LNM, older and male PTMC patients with LNM generally had a higher recurrent rate. In particular, male patients with CLNM tended to have poor prognosis as did older patients with LLNM. One large study found a 2% cause-specific mortality rate after 40 years of follow-up [32]. These findings may be explained by our results and the current staging and risk-stratification system. According to our data, younger age was not associated with postoperative recurrence; nevertheless, even when younger patients had LNM, they were still in stage I, and their risk of postoperative recurrence did not increase. Previous studies have suggested that thyroid cancer is more aggressive in males than in females in terms of tumor recurrence [18]. Therefore, older age and male sex have a negative impact on the prognosis of PTMC patients with LNM. Thus, clinicopathologic factors could be used to determine the appropriate surgical strategy and follow-up plan for PTMC patients with LNM from Guangdong. In addition, more aggressive postoperative treatment (such as RAI) or more frequent follow-up could be considered for older and/or male patients.

Our study has some limitations due to its non-randomized and retrospective design. Moreover, our results may not be applicable to other races or countries. Additionally, due to surgical regulations in early years, not all central or lateral LND was complete, and some LND may have consisted of the removal of solitary or random lymph nodes. Despite these limitations, this study has several strengths. We have provided the basis to assess the risk of different types of LNM and postoperative recurrence in PTMC patients with LNM from Guangdong Province, China. In addition, our study was based on a long-term follow-up of patients of same race and in a relatively local region. Furthermore, we used surgical and pathological data, which are more reliable than findings based on ultrasonography or CT.

In conclusion, PTMC easily metastasizes to the central and lateral lymph nodes, which significantly influences the prognosis of patients from Guangdong. Our results demonstrate that variables associated with both CLNM and LLNM include younger age (<45 years), male sex, larger tumor size (>5 mm), ETE, multifocality and absence of concomitant thyroiditis. Therefore, prophylactic LND is recommended in certain patients from Guangdong, China, who display characteristics associated with a high risk of CLNM and/or LLNM. Given the higher recurrence rate in older (≥45 years) and male patients with LNM, more aggressive postoperative treatment or more frequent follow-up could be considered in these individuals to improve prognosis.

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Disclosure of conflict of interest

None.

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