The American Journal of Surgery 220 (2020) 334–340

Contents lists available at ScienceDirect

The American Journal of Surgery

journal homepage: www.americanjournalofsurgery.com

Predicting factors for central or lateral lymph node metastasis in conventional papillary thyroid microcarcinoma

Lei Sheng [a, 1], Jinyuan Shi [a, b, 1], Bo Han [c], Bin Lv [a], Luchuan Li [a], Bo Chen [a], Nan Liu [a], Yingting Cao [d], Andrew G. Turner [e], Qingdong Zeng [a, *]

[a] Department of Thyroid Surgery, Qilu Hospital of Shandong University, Jinan, Shandong, China
[b] School of Medicine, Shandong University, Jinan, Shondong, China
[c] Department of Pathology, Qilu Hospital of Shandong University, Jinan, Shondong, China
[d] School of Medicine, The University of Adelaide, Adelaide, SA, Australia
[e] UniSA Clinical and Health Sciences, University of South Australia, Adelaide, SA, Australia

ARTICLE INFO

Article history:
Received 21 August 2019
Received in revised form
6 November 2019
Accepted 14 November 2019

Keywords:
Papillary thyroid microcarcinoma
Lymph node metastasis
Risk factors

ABSTRACT

Background: Optimal management for papillary thyroid microcarcinoma (PTMC) remains controversial. The purpose of this study was to explore risk factors predictive of cervical lymph node metastasis in conventional PTMCs.

Methods: Conventional PTMC patients (n = 2,404) undergoing surgery between 2010 and 2017 were grouped and analyzed according to the positivity of cervical lymph node.

Results: Central lymph node (CLN) metastases and lateral lymph node (LLN) metastases were observed in 915 (38.1%) and 184 (7.7%) cases, respectively. Multivariate analysis found that male (odds ratio [OR] = 1.974, $p < 0.001$), younger age (OR = 1.601, $p < 0.001$), tumor size (OR = 1.935, $p < 0.001$), extrathyroidal extension (ETE) (OR = 1.647, $p < 0.001$), multifocality (OR = 1.416, $p < 0.001$), and intrathyroidal spreading (OR = 3.355, $p < 0.001$) predicted increased CLN metastasis. In particular, younger age, multifocality, and intrathyroidal spreading were significantly associated with a high number of CLN metastases ($n \geq 5$). The presence of CLN metastasis was strongly associated with LLN metastasis (OR = 5.426, $p < 0.001$).

Conclusion: Male, younger age, tumor size, ETE, multifocality, and intrathyroidal spreading predict increased CLN metastasis in PTMCs. In patients with suspicious lateral lymphadenopathy, the presence of CLN metastasis is independently associated with LLN metastasis.

Introduction

Over the past several decades, the incidence of thyroid cancer has steadily increased in many countries, although the mortality rate remains stable.[1,2] In the USA, thyroid cancer is the fifth most common cancer in women, with 53,990 estimated new cases in 2018.[3] An ongoing increase in thyroid cancer has also been reported by several studies in China.[4–6] Papillary thyroid cancer (PTC) accounts for over 80% of all new thyroid cancers.[7] Detection of papillary thyroid microcarcinoma (PTMC) (≤10 mm diameter) has correspondingly increased, largely due to population-based routine health assessments with high-resolution ultrasound, and subsequent fine needle aspiration (FNA) biopsy.[5] Despite the increasing incidence of PTMC, the prognosis is usually favorable, with a 10-year survival rate of >99% based on a population-based study that included 29,512 patients.[8] Due to the indolent nature of PTMC, the 2015 American Thyroid Association (ATA) guidelines became more conservative, recommending active surveillance as a reasonable alternative approach to immediate surgery for low-risk PTMC patients willing to comply with a subsequent follow-up plan.[9] However, aggressive features such as gross extrathyroidal extension (ETE) or cervical lymph node invasion present in some PTMC patients indicate an intermediate- or high-risk group not suitable for active surveillance.[10] Whether prophylactic central lymph node dissection (CLND) should be undertaken in PTMC patients remains controversial, as CLND is known to be a risk factor for complications such as hypoparathyroidism and recurrent laryngeal nerve injury.[11]

* Corresponding author. Department of Thyroid Surgery, Qilu Hospital of Shandong University, NO.107 Wenhuaxi Road, Jinan, China.
E-mail address: zqd596@sdu.edu.cn (Q. Zeng).
[1] Equally contributed to this work.

https://doi.org/10.1016/j.amjsurg.2019.11.032
0002-9610/

The rate of central lymph node metastasis has been reported to be 28.6%–64.1% in PTMC patients,[12–14] for whom therapeutic CLND should be encouraged. In addition, lateral lymph node metastasis is also observed in some PTMC patients.[10,13] A high number of positive lymph nodes or a high positive lymph node ratio is associated with increased recurrence rate and reduced long-term survival in PTC patients.[15–18]

The aim of this study was to explore the associations between clinicopathologic factors and central lymph node (CLN) metastasis or lateral lymph node (LLN) metastasis in 2,404 conventional PTMC patients and assess the relative predictive value of these factors.

Materials and methods

Patient selection

We retrospectively reviewed the medical records of 2,404 pathologically proven conventional PTMC patients who underwent lobectomy or total or near-total thyroidectomy and central neck dissection (CND), with or without lateral neck dissection (LND) at the Department of Thyroid Surgery, Qilu Hospital of Shandong University between January 2010 and December 2017. Patients with the following conditions were excluded from the study: a previous history of thyroidectomy, non-PTC carcinomas, non-conventional PTC type, tumor size > 1 cm, or presence of a distant metastasis. A consent form was obtained from each patient involved in this study, and the study approved by the Qilu Hospital ethics committee (Ethical Approval Number: KYLL-2018(KS)-057).

Surgical methods

Lobectomy was performed when a single tumor was confined to a single lobe. Total thyroidectomy was performed when multifocality, tumor bilaterility, extrathyroidal extension (ETE), or abnormal lymphadenopathy was detected during the preoperative or intraoperative examination. CND was defined as a level of VI dissection including pre- and paratracheal nodes, precricoid nodes, perithyroidal nodes, and lymph nodes along recurrent laryngeal nerves. CND was performed on all pathologically proven conventional PTMC patients. LND was defined as the excision of the lateral neck lymph nodes including modified radical neck dissection and selective neck dissection. Modified radical neck dissection refers to the excision of lateral neck lymph nodes including levels II-V. Selective neck dissection refers to cervical lymphadenectomy in which there is preservation of one or more of the lateral lymph node groups. Therapeutic LND was performed in cases with biopsy-proven or ultrasound-suspicious lateral cervical lymphadenopathy.

Histopathologic examination with surgical specimens

Surgical specimens were microscopically examined by two or more experienced pathologists. Histopathologic examination included the cell type of the main lesion, the primary tumor size (measured as the longest diameter of the largest lesion), multifocality, ETE, lymphovascular invasion, intrathyroidal spreading, regional lymph node metastasis, and underlying conditions of the thyroid such as chronic lymphocytic thyroiditis (CLT) and nodular goiter. Multifocality was defined as having two or more lesions of PTMC in a single lobe or two lobes. Intrathyroidal spreading referred to a major thyroid carcinoma with surrounding scattered small lesions, with features of heterotypic cells, psammoma bodies, and lymphatic vessel invasion.[19]

BRAF V600E mutation analysis

BRAF V600E mutation analysis was performed at the Molecular Diagnostic Laboratory of Qilu Hospital. DNA samples for molecular analysis were extracted from postoperative surgical specimens using AmoyDx® FFPE DNA extraction kit (Amoy Diagnostics, Xiamen, China). *BRAF* V600E mutation status was assessed with Human *BRAF* V600E mutation Fluorescence Polymerase Chain Reaction (PCR) Diagnostic Kit (Amoy Diagnostics, Xiamen, China) using the Agilent-Stratagene M×3000P Q-PCR system (Agilent Technologies, Santa Clara, CA), according to the manufacturers' instructions.[20]

Statistical analysis

Statistical analyses were performed using SPSS version 17 software (IBM Corp, NY, USA), and statistically significant differences were defined as those with a p value less than 0.05. Continuous variables were presented as mean ± standard deviation (SD). For categorical variables, the number and percentage (%) of cases are presented, as well as the odds ratio (OR). Chi-square tests were used for categorical variables and Student's t-test for continuous variables. Multivariate analysis was carried out on the variables with p-values of <0.05 in the univariate analysis. For the multivariate analysis, multiple logistic regression was used to determine whether the clinicopathologic characteristics were independent predictors for central or lateral lymph node metastasis in conventional PTMC patients.

Results

Baseline clinicopathologic characteristics of 2,404 conventional PTMC patients

Of the 2,404 PTMC patients studied, 506 (21.0%) were men and 1,898 (79.0%) were women (Table 1). A total of 334 cases had clinically positive lymph nodes (13.9%). The mean age was 44.6 years with 1,134 (47.2%) patients being older than 45 years. All

Table 1
Clinicopathologic characteristics of 2,404 conventional PTMC patients.

Clinicopathologic features	CND group	LND group
Total	n = 2,404(%)	n = 248(%)
Sex		
Female	1,898(79.0)	186(75.0)
Male	506(21.0)	62(25.0)
Age(years)		
mean ± SD	44.6 ± 10.5	42.4 ± 11.3
≤45	1270(52.8)	151(60.9)
>45	1134(47.2)	97(39.1)
Tumor size (mm)		
mean ± SD	6.6 ± 2.2	7.3 ± 2.3
≤5	823(34.2)	62(25.0)
>5,≤10	1,581(65.8)	184(74.2)
Total number of LN dissected (mean ± SD)	4.9 ± 3.9	15.7 ± 9.7
Average positive LN number (mean ± SD)	2.4 ± 2.2	3.8 ± 2.9
Number of patients with positive LN	915(38.1)	184(74.2)
ETE	779(32.4)	112(45.2)
Multifocality	709(29.5)	98(39.5)
Lymphovascular invasion	15(0.6)	3(1.2)
CLT	462(19.2)	49(19.8)
Nodular goiter	787(32.7)	86(34.7)
BRAF mutation tested	644(26.8)	80(32.3)
BRAF mutation positivity	548(85.1)	72(90.0)

PTMC: Papillary Thyroid Microcarcinoma; CND: Central Neck Dissection; LND: Lateral Neck Dissection; SD: Standard Deviation; LN: Lymph Node; ETE: Extrathyroidal Extension; CLT: Chronic Lymphocytic Thyroiditis.

enrolled patients underwent CND and 248 (10.3%) patients underwent either modified radical or selective LND. Lobectomy was performed in 1,321 (55.0%) patients, while total or near-total thyroidectomy was performed in 1,083 (45.0%) patients. *BRAF* V600E mutation status was available for 644 (26.8%) patients with a positive result observed in 548 (85.1%) patients. Mean tumor size was 6.6 mm and 823 tumors (34.2%) were smaller than 5 mm. Multifocality, ETE, lymphovascular invasion, intrathyroidal spreading, and CLT were observed in 709 (29.5%), 779 (32.4%), 15 (0.6%), 87 (3.6%) and 462(19.2%) cases, respectively (Table 1).

Of the 248 clinically node-positive PTMC patients undergoing LND, positive LLNs were confirmed by histopathological sections in 184 (74.2%) cases (Table 1). Sixty-two cases (25.0%) were men and 186 (75.0%) were women. The mean age was 42.4 years with 97 (39.1%) patients being older than 45 years. *BRAF* V600E mutation status was available for 80 (32.3%) cases, with 72 (90%) being positive. The mean tumor size was 7.3 mm and 62 (25.0%) of PTMCs had a diameter smaller than 5 mm. Multifocality, ETE, lymphovascular invasion, and CLT was observed in 98 (39.5%), 112 (45.2%), 3 (1.2%), and 49 (19.8%) cases, respectively (Table 1).

Conventional open surgery, modified Miccoli's surgery, or endoscopic surgery was performed in 2,247 (93.5%), 79 (3.3%), and 78 (3.2%) patients (Table 2). Among the 2,404 patients, 958 (39.9%) had cervical lymph node metastasis. CLN metastasis was found in 915 (38.1%) cases. Of these, 141 (5.9%) had both CLN and LLN metastasis, and 43 (1.8%) had skip metastasis to the LLN only (Table 2).

Association between clinicopathologic characteristics and CLN metastasis in 2,404 conventional PTMC patients

CLN metastasis was found in 915 (38.1%) patients (Table 3). Univariate analysis revealed significant associations with male ($p < 0.001$), age less than 45 years ($p < 0.001$), a large tumor size ($p < 0.001$), ETE ($p < 0.001$), multifocality ($p < 0.001$), lymphovascular invasion ($p < 0.05$), and intrathyroidal spreading ($p < 0.001$), while CTL ($p < 0.001$) was associated with less CLN metastasis (Table 3). Multivariate analyses indicated male (adjusted OR = 1.974, $p < 0.001$), age less than 45 years (adjusted OR = 1.601, $p < 0.001$), a large tumor size (adjusted OR = 1.935, $p < 0.001$), ETE (adjusted OR = 1.647, $p < 0.001$), multifocality (adjusted OR = 1.416, $p < 0.001$), and intrathyroidal spreading (adjusted OR = 3.355, $p < 0.001$) were independent predictors for more CLN metastasis, while CTL (adjusted OR = 0.731, $p < 0.01$) was shown to be an independent predictor for less CLN metastasis (Table 3). We further analyzed the association between clinicopathologic characteristics and CLN metastasis in 2,070 of clinically node-negative PTMC patients and similar results observed (Supplementary Table 1).

BRAF V600E mutation status was available in 644 (26.8%) conventional PTMC patients. *BRAF* V600E mutation positivity was found in 239 (86.3%) patients with CLN metastasis and in 309 (84.2%) patients with negative CLN, indicating that *BRAF* mutation was common but not associated with CLN metastasis (Table 3).

As previous studies have shown a high volume of metastatic lymph nodes or increased positive lymph node ratio may be associated with increased risk of disease recurrence,[21,22] we tested the association between clinicopathologic characteristics and the number of metastatic lymph nodes greater than 5. Multivariate analysis indicated that younger age, multifocality, and intrathyroidal spreading were significantly associated with a high number of metastatic central lymph nodes (Table 4).

Association between clinicopathologic characteristics and LLN metastasis in 248 conventional PTMC patients

LND was undertaken in 248 (10.3%) patients with suspicious lateral lymph node by preoperative ultrasound (Table 5). In univariate analysis, large tumor size ($p < 0.05$), ETE ($p < 0.05$), multifocality ($p < 0.05$), intrathyroidal spreading ($p < 0.05$), and CLN metastasis ($p < 0.001$) were significantly associated with LLN metastasis, while other clinicopathologic factors (male, age, lymphovascular invasion, CLT, and *BRAF* V600E mutation) were not associated with LLN metastasis. In multivariate analysis, only CLN metastasis (adjusted OR = 5.426, $p < 0.001$) was strongly associated with LLN metastasis, while large tumor size, multifocality, ETE, and intrathyroidal spreading had no significant relationship with LLN metastasis (Table 5).

Association between clinicopathologic features and BRAF V600E mutation in 644 conventional PTMC patients

In univariate analysis, the *BRAF* V600E mutation was significantly associated with ETE ($p < 0.001$), CLT ($p < 0.05$), and nodular goiter ($p < 0.05$), but not associated with other clinicopathologic factors (sex, age, lymphovascular invasion, multifocality, and intrathyroidal spreading) (Supplementary Table 2). In multivariate analysis, the *BRAF* V600E mutation was significantly associated with ETE ($p < 0.001$).

Table 2
Extent of surgery and frequency of lymph node metastasis in 2,404 patients with conventional PTMC.

	n (total = 2,404)	%
Extent of surgery		
Lobectomy	1321	55.0
Total or near-total thyroidectomy	1083	45.0
Type of surgery		
Open surgery	2247	93.5
Modified Miccoli's surgery	79	3.3
Endoscopic surgery	78	3.2
LNM		
No lymph node metastasis	1,446	60.1
CLNM only	774	32.2
CLNM and LLNM	141	5.9
LLNM without CLNM	43	1.8

LNM: Lymph Node Metastasis; CLNM: Central Lymph Node Metastasis; LLNM: Lateral.
Lymph Node Metastasis.

Discussion

While therapeutic lymph node dissection is a standard approach for PTMC with clinically involved lymphadenopathy, prophylactic CLND remains controversial for low-risk PTMC patients in the absence of clinically detectable abnormal lymph nodes. Although patients with PTMC have a favorable prognosis, the presence of lymph node metastasis is believed to be associated with poor prognosis.[21,22] In this study, we comprehensively analyzed the frequency and pattern of cervical lymph node metastasis in 2,404 patients with PTMC from a single medical center over 8 years, with the prevalence of CLN and LLN metastasis being 38.1% (915 of 2,404) and 7.7% (184 of 2,404), respectively. In our study, we found that male gender, younger age (≤45 years), tumor size, ETE, multifocality, and intrathyroidal spreading were risk factors for CLN metastasis.

Table 3
Association between clinicopathologic characteristics and CLN metastasis in PTMC patients.

Clinicopathologic features	CLN Negative NO. (%)	CLN Positive NO. (%)	*p value*	Multivariate Analysis*	
				Adjusted OR (95%CI)	*p value*
Total	1,489(61.9)	915(38.1)	NA	NA	NA
Sex					
Female	1,244(83.5)	654(71.5)		Ref.	
Male	245(16.5)	261(28.5)	<0.001	1.974(1.600–2.436)	<0.001
Age (years)					
>45	765(51.4)	369(40.3)		Ref.	
≤45	724(48.6)	546(59.7)	<0.001	1.601(1.343–1.909)	<0.001
Tumor size (mm)					
≤5	607(40.8)	216(23.6)		Ref.	
>5,≤10	882(59.2)	699(76.4)	<0.001	1.935(1.596–2.347)	<0.001
ETE					
Absent	1087(73.0)	538(58.8)		Ref.	
Present	402(27.0)	377(41.2)	<0.001	1.647(1.367–1.986)	<0.001
Multifocality					
Absent	1,098(73.7)	597(65.2)		Ref.	
Present	391(26.3)	318(34.8)	<0.001	1.416(1.172–1.710)	<0.001
Lymphovascular invasion					
Absent	1,484(99.7)	905(98.9)		Ref.	
Present	5(0.3)	10(1.1)	0.031	1.414(0.448–4.467)	0.555
Intrathyroidal spreading					
Absent	1,466(98.5)	851(93.0)		Ref.	
Present	23(1.5)	64(7.0)	<0.001	3.355(2.023–5.564)	<0.001
CLT					
Absent	1,170(78.6)	772(84.4)		Ref.	
Present	319(21.4)	143(15.6)	<0.001	0.731(0.581–0.920)	0.008
Nodular goiter					
Absent	988(66.4)	629(68.7)		NA	NA
Present	501(33.6)	286(31.3)	0.225	NA	NA
BRAF mutation					
Negative	58(15.8)	38(13.7)		NA	NA
Positive	309(84.2)	239(86.3)	0.462	NA	NA

PTMC: Papillary Thyroid Microcarcinoma; CLN: Central Lymph Node; OR: Odds Ratio; CI: Confidence Interval; NA: Not Available; ETE: Extrathyroidal Extension; CLT: Chronic Lymphocytic Thyroiditis.
*Variables that reached $p < 0.05$ in univariate analysis were included.

Gender and age

Previous studies have consistently shown that men with PTMC are at greater risk of CLN metastasis.[14,23–25] Our study also indicated male gender was an independent predictor of CLN metastasis, but not a risk factor for LLN metastasis.

Three previous studies in smaller cohorts of Korean patients with PTMC found age was not associated with risk of CLN metastasis.[23,24,26] However, our study indicated that age (≤45 years) was an independent predictor of CLN metastasis in conventional PTMC (OR = 1.601, 95%CI, 1.343–1.909), and this is consistent with two previous Chinese studies including 1,066 and 1,304 cases of PTMC, respectively.[14,25] Moreover, in the current study age predicted a high volume of positive CLN (n ≥ 5). Thus, these data support routine CLND being encouraged for younger Chinese PTMC patients.

Tumor size

In our PTMC patients, tumor size (>0.5 cm) was an independent risk factor for CLN metastasis. Similarly most previous studies have reported that larger tumor diameter (>0.5 cm) is associated with CLN metastasis,[14,24,25,27] while only one study indicated no correlation between tumor size and CLN metastasis after multivariate analysis.[23]

Extrathyroidal extension

Our observation that ETE was significantly associated with central lymph node metastasis is comparable with other reports describing cases of PTMCs.[23–25] However, ETE was not associated with a high volume of positive CLN (n ≥ 5) or LLN metastasis.

Multifocality and intrathyroidal spreading

Consistent with previous reports that multifocality predicts CLN metastasis,[14,23–25] we found multifocality to be associated with CLN metastasis in our cohort of PTMC patients. We also found that having greater than 5 positive CLNs was associated with multifocality in PTMC patients. The relationship between multifocality and LLN metastasis remains less equivocal. In our cohort, multifocality was not associated with LLN metastasis. However, a previous study including 1,066 Chinese PTMC patients suggested multifocality was associated with LLN metastasis.[25]

Genetic studies indicate some multifocal papillary cancers arise from intrathyroidal spreading of a single cancer.[28,29] In this study, cancers with scattering foci only detectible by microscopy were classified as PTMC with intrathyroidal spreading. PTMCs with the feature of intrathyroidal spreading tend to have an increased risk for LLN metastasis. However, in our study this was not statistically significant after adjusting for other risk factors, and this was consistent with a recent study showing intrathyroidal spreading to be not associated with LLN metastasis risk for papillary thyroid cancer.[30] Based on currently available evidence, both multifocality and intrathyroidal spreading are independent predictors for CLN metastasis. However, the impact of these two factors on the LLN metastasis largely remains an open question and warrants further

Table 4
Association between clinicopathologic characteristics and metastatic CLN number greater than 5 in PTMC patients.

Clinicopathologic features	Positive LN < 5 (%)	Positive LN ≥ 5 (%)	*p value*	Multivariate Analysis*	
				Adjusted OR (95%CI)	*p value*
Total	799(87.3)	116(12.7)	NA	NA	NA
Sex					
Female	577(72.2)	77(66.4)		NA	NA
Male	222(27.8)	39(33.6)	0.194	NA	NA
Age (years)					
>45	332(41.6)	37(31.9)		Ref.	
≤45	467(58.4)	79(68.1)	0.049	1.57(1.01–2.42)	0.043
Tumor size (mm)					
≤5	197(24.7)	19(16.4)		Ref.	
>5,≤10	602(75.3)	97(83.6)	0.052	1.25(0.73–2.14)	0.426
ETE					
Absent	485(60.7)	53(45.7)		Ref.	
Present	314(39.3)	63(54.3)	0.002	1.52(0.99–2.30)	0.510
Multifocality					
Absent	537(67.2)	60(51.7)		Ref.	
Present	262(32.8)	56(48.3)	0.001	1.98(1.31–3.00)	0.001
Lymphovascular invasion					
Absent	792(99.1)	113(97.4)		NA	NA
Present	7(0.9)	3(2.6)	0.115	NA	NA
Intrathyroidal spreading					
Absent	759(95.0)	92(79.3)		Ref.	
Present	40(5.0)	24(20.7)	<0.001	4.43(2.50–7.86)	<0.001
CLT					
Absent	676(84.6)	96(82.8)		NA	NA
Present	123(15.4)	20(17.2)	0.609	NA	NA
Nodular goiter					
Absent	546(68.3)	83(71.6)		NA	NA
Present	253(31.7)	33(28.4)	0.485	NA	NA
BRAF mutation					
Negative	34(14.4)	4(9.8)		NA	NA
Positive	202(85.6)	37(90.2)	0.428	NA	NA

PTMC: Papillary Thyroid Microcarcinoma; CLN: Central Lymph Node; OR: Odds Ratio; CI: Confidence Interval; NA: Not Available; ETE: Extrathyroidal Extension; CLT: Chronic Lymphocytic Thyroiditis.
*Variables that reached $p < 0.05$ in univariate analysis were included.

investigation.

BRAF mutation

The *BRAF* gene mutation is common in PTC, ranging from 34% to 85%.[31] In our study, 85.1% of PTMC patients had the *BRAF* mutation, closely matching the rate in another study with a Chinese patient group.[14] The *BRAF* mutation has been considered a molecular biomarker associated with worse prognosis for PTC. However, existing data are inconsistent regarding the association of the *BRAF* gene mutation and CLN metastasis,[14,31,32] largely due to variable mutation rates and surgical approaches among patients. Although this study indicated an association between the *BRAF* gene mutation and extrathyroidal extension, no correlation was found between the *BRAF* mutation and cervical lymph node metastasis.

Coexisting chronic lymphocytic thyroiditis (CLT)

Elevated levels of thyroid-stimulating hormone (TSH), especially in conjunction with CLT, are considered a risk factor for the development of thyroid malignancy and have been associated with a more advanced status of PTC.[33] However, the data regarding the impact of CLT on cervical lymph node metastasis in PTC were inconsistent. Some studies have shown more lymph node metastasis in PTC patients with CLT,[34,35] but others less.[36–38] Two studies focusing on PTMC patients found no association between the coexistence of CLT and CLN metastasis.[14,39] In contrast, in this study coexisting CLT was observed in 19.2% of PTMC patients we studied and was an independent predictor of less CLN metastasis.

Limitations

The aim of this large retrospective study was to identify risk factors for cervical lymph node metastasis in PTMC patients, however long-term follow-up data for complications, recurrence, and mortality are not available. We were able to analyze *BRAF* gene mutation status in our cohort, but not other genetic factors, tumor location, or ultrasound features that may impact on cervical lymph node metastasis. Lateral lymph node dissection was not routinely performed for all PTMC patients, with the rate of LLN metastasis observed in this study lower than expected.

Conclusions

In conclusion, our data indicate that male gender, younger age (≤45 years), tumor size (>5 mm), ETE, multifocality, and intrathyroidal spreading may predict CLN metastasis in conventional PTMC patients, while coexisting CLT was associated with less CLN metastasis. In particular, younger age, multifocality, and intrathyroidal spreading were associated with a high volume of positive CLNs (n ≥ 5). In contrast, *BRAF* gene mutation was not a risk factor for CLN metastasis. The presence of positive CLNs was strongly associated with LLN metastasis for patients with suspicious lateral lymphadenopathy diagnosed by pre-operative imaging. Taken together, these data may indicate some PTMC patients requiring closer surveillance and ultimately surgical intervention.

Table 5
Association between clinicopathologic characteristics and LLN metastasis in PTMC patients.

Clinicopathologic features	LLN Negative NO. (%)	LLN Positive NO. (%)	*p value*	Multivariate Analysis*	
				Adjusted OR (95%CI)	*p value*
Total	64(25.8)	184(74.2)		NA	NA
Sex					
Female	51(79.7)	135(73.4)			
Male	13(20.3)	49(26.6)	0.316	NA	NA
Age (years)					
≤45	35(54.7)	116(63.0)			
>45	29(45.3)	68(37.0)	0.239	NA	NA
Tumor size (mm)					
≤5	22(34.4)	40(21.7)		Ref.	
>5,≤10	42(65.6)	144(78.3)	0.046	1.424(0.700–2.895)	0.329
ETE					
Absent	43(67.2)	93(50.5)			
Present	21(32.8)	91(49.5)	0.022	1.529(0.784–2.982)	0.213
Multifocality					
Absent	46(71.9)	104(56.5)		Ref.	
Present	18(28.1)	80(43.5)	0.032	1.379(0.695–2.737)	0.357
Lymphovascular invasion					
Absent	63(98.4)	182(98.9)			
Present	1(1.6)	2(1.1)	0.766	NA	NA
Intrathyroidal spreading					
Absent	63(98.4)	163(88.6)		Ref.	
Present	1(1.6)	21(11.4)	0.043	3.860(0.481–31.000)	0.204
CLN metastasis					
Absent	42(65.6)	43(23.4)			
Present	22(34.4)	141(76.6)	<0.001	5.426(2.879–10.226)	<0.001
CLT					
Absent	52(81.2)	147(79.9)			
Present	12(18.8)	37(20.1)	0.814	NA	NA
Nodular goiter					
Absent	46(71.9)	116(63.0)			
Present	18(28.1)	68(37.0)	0.203	NA	NA
BRAF mutation					
Negative	2(11.8)	6(9.5)			
Positive	15(88.2)	57(90.5)	0.785	NA	NA

PTMC: Papillary Thyroid Microcarcinoma; LLN: Lateral Lymph Node; OR: Odds Ratio; CI: Confidence Interval; NA: Not Available; ETE: Extrathyroidal Extension; CLT: Chronic Lymphocytic Thyroiditis.
*Variables that reached $p < 0.05$ in univariate analysis were included.

Declaration of competing interest

The authors have no conflict of interest to disclose.

Acknowledgments

This work was supported by the National Natural Science Foundation of China (Grant NO. 81802642).

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.amjsurg.2019.11.032.

References

1. James BC, Mitchell JM, Jeon HD, et al. An update in international trends in incidence rates of thyroid cancer, 1973-2007. *Cancer Causes Control*. 2018;29:465–473.
2. Pellegriti G, Frasca F, Regalbuto C, et al. Worldwide increasing incidence of thyroid cancer: update on epidemiology and risk factors. *J Cancer Epidemiol*. 2013:965212, 2013.
3. Siegel RL, Miller KD, Jemal A. Cancer statistics. *CA A Cancer J Clin*. 2018;68:7–30, 2018.
4. Wang Y, Wang W. Increasing incidence of thyroid cancer in Shanghai, China, 1983-2007. *Asia Pac J Public Health*. 2015;27:223–229.
5. Du L, Wang Y, Sun X, et al. Thyroid cancer: trends in incidence, mortality and clinical-pathological patterns in Zhejiang Province, Southeast China. *BMC Canc*. 2018;18:291.
6. Xie SH, Chen J, Zhang B, et al. Time trends and age-period-cohort analyses on incidence rates of thyroid cancer in Shanghai and Hong Kong. *BMC Canc*. 2014;14:975.
7. Kitahara CM, Sosa JA. The changing incidence of thyroid cancer. *Nat Rev Endocrinol*. 2016;12:646–653.
8. Wang TS, Goffredo P, Sosa JA, et al. Papillary thyroid microcarcinoma: an over-treated malignancy? *World J Surg*. 2014;38:2297–2303.
9. Haugen BR, Alexander EK, Bible KC, et al. American Thyroid Association management guidelines for adult patients with thyroid nodules and differentiated thyroid cancer: the American Thyroid Association guidelines task force on thyroid nodules and differentiated thyroid cancer. *Thyroid*. 2015;26:1–133, 2016.
10. Nie X, Tan Z, Ge M. Skip metastasis in papillary thyroid carcinoma is difficult to predict in clinical practice. *BMC Canc*. 2017;17:702.
11. Mazzaferri EL, Doherty GM, Steward DL. The pros and cons of prophylactic central compartment lymph node dissection for papillary thyroid carcinoma. *Thyroid*. 2009;19:683–689.
12. Liu W, Cheng R, Su Y, et al. Risk factors of central lymph node metastasis of papillary thyroid carcinoma: a single-center retrospective analysis of 3273 cases. *Medicine (Baltim)*. 2017;96, e8365.
13. Wada N, Duh QY, Sugino K, et al. Lymph node metastasis from 259 papillary thyroid microcarcinomas: frequency, pattern of occurrence and recurrence, and optimal strategy for neck dissection. *Ann Surg*. 2003;237:399–407.
14. Zhang Q, Wang Z, Meng X, et al. Predictors for central lymph node metastases in CN0 papillary thyroid microcarcinoma (mPTC): a retrospect analysis of 1304 cases. *Asian J Surg*. 2018.
15. Lang BH, Ng SH, Lau LL, et al. A systematic review and meta-analysis of prophylactic central neck dissection on short-term locoregional recurrence in papillary thyroid carcinoma after total thyroidectomy. *Thyroid*. 2013;23:1087–1098.
16. Schneider DF, Chen H, Sippel RS. Impact of lymph node ratio on survival in papillary thyroid cancer. *Ann Surg Oncol*. 2013;20:1906–1911.
17. Amit M, Tam S, Boonsripitayanon M, et al. Association of lymph node density with survival of patients with papillary thyroid cancer. *JAMA Otolaryngol Head Neck Surg*. 2018;144:108–114.
18. Lee YC, Na SY, Park GC, et al. Occult lymph node metastasis and risk of regional recurrence in papillary thyroid cancer after bilateral prophylactic central neck dissection: a multi-institutional study. *Surgery*. 2017;161:465–471.

19. Jin H, Yan H, Tang H, et al. Internal spreading of papillary thyroid carcinoma: a case report and systemic review. *Case Rep Endocrinol*. 2018;2018:7618456.
20. Ye J-X, Liu Y, Qin Y, et al. KRAS and BRAF gene mutations and DNA mismatch repair status in Chinese colorectal carcinoma patients. *World J Gastroenterol: WJG*. 2015;21:1595.
21. Grogan RH, Kaplan SP, Cao H, et al. A study of recurrence and death from papillary thyroid cancer with 27 years of median follow-up. *Surgery*. 2013;154:1436–1447.
22. Vas Nunes JH, Clark JR, Gao K, et al. Prognostic implications of lymph node yield and lymph node ratio in papillary thyroid carcinoma. *Thyroid*. 2013;23:811–816.
23. So YK, Son YI, Hong SD, et al. Subclinical lymph node metastasis in papillary thyroid microcarcinoma: a study of 551 resections. *Surgery*. 2010;148:526–531.
24. Chang YW, Kim HS, Kim HY, et al. Should central lymph node dissection be considered for all papillary thyroid microcarcinoma? *Asian J Surg*. 2016;39:197–201.
25. Zhang L, Wei WJ, Ji QH, et al. Risk factors for neck nodal metastasis in papillary thyroid microcarcinoma: a study of 1066 patients. *J Clin Endocrinol Metab*. 2012;97:1250–1257.
26. Park JP, Roh JL, Lee JH, et al. Risk factors for central neck lymph node metastasis of clinically noninvasive, node-negative papillary thyroid microcarcinoma. *Am J Surg*. 2014;208:412–418.
27. Lim YC, Choi EC, Yoon YH, et al. Central lymph node metastases in unilateral papillary thyroid microcarcinoma. *Br J Surg*. 2009;96:253–257.
28. Park SY, Park YJ, Lee YJ, et al. Analysis of differential BRAFV600E mutational status in multifocal papillary thyroid carcinoma: evidence of independent clonal origin in distinct tumor foci. *Cancer*. 2006;107:1831–1838.
29. Jovanovic L, Delahunt B, McIver B, et al. Most multifocal papillary thyroid carcinomas acquire genetic and morphotype diversity through subclonal evolution following the intra-glandular spread of the initial neoplastic clone. *J Pathol*. 2008;215:145–154.
30. Zhao H, Huang T, Li H. Risk factors for skip metastasis and lateral lymph node metastasis of papillary thyroid cancer. *Surgery*. 2019:1–6.
31. Song JY, Sun SR, Dong F, et al. Predictive value of BRAF(V600E) mutation for lymph node metastasis in papillary thyroid cancer: a meta-analysis. *Curr Med Sci*. 2018;38:785–797.
32. Jung CK, Kang YG, Bae JS, et al. Unique patterns of tumor growth related with the risk of lymph node metastasis in papillary thyroid carcinoma. *Mod Pathol*. 2010;23:1201–1208.
33. Nagayama Y. Thyroid autoimmunity and thyroid cancer - the pathogenic connection: a 2018 update. *Horm Metab Res*. 2018;50:602–608.
34. Konturek A, Barczyński M, Wierzchowski W, et al. Coexistence of papillary thyroid cancer with Hashimoto thyroiditis. *Langenbeck Arch Surg*. 2013;398:389–394.
35. Shen CT, Zhang XY, Qiu ZL, et al. Thyroid autoimmune antibodies in patients with papillary thyroid carcinoma: a double-edged sword? *Endocrine*. 2017;58:176–183.
36. Dvorkin S, Robenshtok E, Hirsch D, et al. Differentiated thyroid cancer is associated with less aggressive disease and better outcome in patients with coexisting Hashimotos thyroiditis. *J Clin Endocrinol Metab*. 2013;98:2409–2414.
37. Zhu F, Shen YB, Li FQ, et al. The effects of hashimoto thyroiditis on lymph node metastases in unifocal and multifocal papillary thyroid carcinoma: a retrospective Chinese cohort study. *Medicine (Baltim)*. 2016;95, e2674.
38. Ieni A, Vita R, Magliolo E, et al. One-third of an archivial series of papillary thyroid cancer (years 2007–2015) has coexistent chronic lymphocytic thyroiditis, which is associated with a more favorable tumor-node-metastasis staging. *Front Endocrinol*. 2017;8:337.
39. Kim KE, Kim EK, Yoon JH, et al. Preoperative prediction of central lymph node metastasis in thyroid papillary microcarcinoma using clinicopathologic and sonographic features. *World J Surg*. 2013;37:385–391.