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RESEARCH ARTICLE

Predictive factors for central lymph node and lateral cervical lymph node metastases in papillary thyroid carcinoma

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Abstract

Background Central lymph node metastasis (LNM) in papillary thyroid carcinoma (PTC) is common. But the association between primary tumor characteristics and specific features of metastatic lymph nodes in PTC has not been fully identified. Determining risk factors for LNM may help surgeons determine rational extent of lymph node dissection.

Methods Data from 432 patients who underwent thyroidectomy with cervical lymph node dissection for PTC were retrospectively analyzed. The relationships between LNM to central compartment or lateral compartment and clinicopathologic factors were analyzed. Cox regression model was used to determine the risk factors for recurrence-free survival (RFS).

Results Central lymph node metastasis (CLNM) and lateral lymph node metastasis (LLNM) were found in 216 (50.0%) and 65 (15.0%) patients, respectively. In the multivariate analysis for CLNM, patients < 45 years of age (OR 2.037, 95% CI 1.388–2.988, $P < 0.001$), extrathyroidal invasion (OR: 2.144, 95% CI 0.824–5.457, $P = 0.011$), vascular invasion (OR 13.817, 95% CI 1.694–112.693, $P = 0.014$), LLNM (OR 2.851, 95% CI 1.196–6.797, $P = 0.014$) and TNM Stage III–IV (OR 465.307, 95% CI 113.903–1900.826, $P < 0.001$) were independent predictors for high prevalence of CLNM. In the multivariate analysis for LLNM, tumor size more than 1cm (OR 3.474, 95% CI 1.728–6.985, $P < 0.001$) and CLNM (OR 5.532, 95% CI 2.679–11.425, $P < 0.001$) were independent predictors for high prevalence of LLNM. Moreover, tumor with T3–T4 stage, extrathyroidal invasion and CLNM were the significant factors related to the RFS.

Conclusion For patients with pre-operative risk factors of LNM, an accurate preoperative evaluation of central compartment or lateral compartment is needed to find suspicious lymph nodes. And prophylactic lymph node dissection should be performed in patients with high risk of CLNM. Moreover, we suggest performing close follow-up for patients with high risk of RFS.

Keywords Papillary thyroid carcinoma · Lymph node metastases · Extrathyroidal invasion · Vascular invasion · Recurrence · Recurrence-free survival

Introduction

Over the past few decades, the incidence of thyroid cancer (TC), specially papillary thyroid cancer (PTC), is rising at the fastest rate of all malignancies [1, 2]. PTC is generally indolent but very frequently metastasizes to the regional lymph nodes, including central and lateral compartments. The incidence of lymph node metastases (LNM) in cases of PTC has been reported to range from 30 to 80% [3, 4, 5]. Some studies have reported that LNM is a poor prognostic factor [6, 7, 8].

For patients with central lymph node metastasis (CLNM) or lateral lymph node metastases (LLNM) detected by preoperative ultrasonography (US) or physical examination, therapeutic lymph node dissection is advocated [9]. However, there is no consensus on the indications for prophylactic lymph node dissection. The American Thyroid Association (ATA) suggest that prophylactic central neck dissection (CND) should be performed in PTC patients with T3 or T4 stage [10], while the National Comprehensive Cancer Network (NCCN) guideline indicates prophylactic CND for patients aged less than15 or more than 45 years, with

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tumors more than 4 cm in diameter or with extrathyroidal extension [11]. Besides, the appropriate extent of prophylactic lymph node dissection remains controversial. Radical surgery, such as lateral neck dissection (LND), may injury the spinal accessory nerve or the cervical plexus, which lead to clinically important postoperative morbidities (shoulder dysfunction, neck numbness, and neuropathic pain) [12, 13]. Therefore, assessing high-risk patients with LNM is essential to perform individualized treatment and to avoid the unnecessary prophylactic lymph node dissection.

To find the optimal management of cervical lymph node (LN) in PTC patients, we investigated the risk factors for LNM in the central compartment and lateral compartment by using a large series of patients with surgically proven PTC. Besides, the correlation between LNM and recurrence-free survival (RFS) was also investigated.

Materials and methods

Patients

This retrospective study was approved by the Institutional Review Board of Changzhou First People's Hospital. All participants gave written informed consent for their clinical records to be used in this study. A total of 487 patients with pathologically proven thyroid carcinoma who underwent thyroidectomy from January 2012 to April 2018 at the Changzhou First People's Hospital were retrospectively reviewed from our department prospective surgical database. Patients were excluded from the study if they have any of the following factors: (1) had another malignancy before thyroidectomy; (2) reoperation; (3) non-PTCs (medullary/follicular/anaplastic) or mixed- type PTC; (4) distant metastasis at diagnosis; (5) had upper mediastinal node metastasis detected before thyroidectomy; (6) underwent non-curative surgery. In total, 432 patients were finally included and evaluated.

Surgical procedures

During the first clinical visit, body mass index (BMI) (kg/m^2) was calculated via weight (kg) divided by height (m) squared. Based on the standardized guidelines set by the World Health Organization, enrolled PTC patients were categorized as normal (BMI < 25 kg/m^2) and overweight (25 ≤ BMI kg/m^2). We used the following protocol for surgical procedures (Fig. 1). All patients underwent ultrasonography (US), fine-needle aspiration (FNA) or Computed tomography (CT) to evaluate their primary lesions and lymph node metastasis. For clinically positive LLNM or intraoperative suspected LLNM, total thyroidectomy (TT) with CND and therapeutic ipsilateral LND was undertaken. LND was not performed in cN0 PTC patients (absence of any pre- or intraoperative evidence of lymph node disease), while prophylactic CND was performed in all cN0 PTC patients. Unilateral thyroid lobectomy and CND were performed for unilateral PTC patients while TT and CND were performed for bilateral PTC patients. LND was performed in the usual fashion from at least level II to level V, sparing the internal jugular vein, spinal accessory nerve, and sternocleidomastoid muscle [14]. CND included prelaryngeal, pretracheal and both the right and left paratracheal nodal basins [15]. All lymph nodes specimens were separated by the surgeon according to neck levels, and were sent to the department of pathology for paraffin fixation and histological analysis.

Histopathologic examination of surgical specimens

Two or more experienced pathologists microscopically reviewed and cross-checked all pathology specimens. Primary tumor characteristics were assessed, including histologic subtype, primary tumor size (measured as the longest diameter of the largest lesion), extrathyroidal invasion (defined as neoplastic infiltration beyond the thyroid fibrous capsule), multifocality (defined as two or more PTC lesions in a single lobe), vascular invasion, regional LNM and BRAF mutation. Micro-PTC was defined as PTC ≤ 10 mm

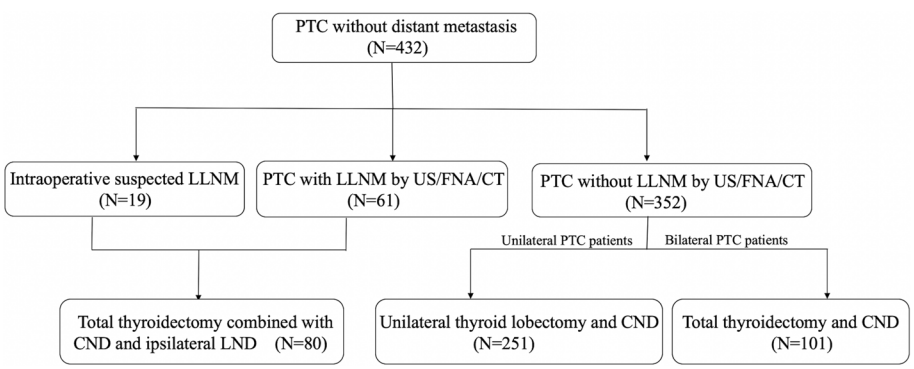

Fig. 1 Flowchart depicting the protocol used in this study. *PTC* papillary thyroid carcinoma, *LLNM* lateral lymph node metastasis, *US* ultrasonography, *FNA* fine-needle aspiration, *CT* Computed tomography, *CND* central neck dissection, *LND* lateral neck dissection

in its maximum diameter while Macro-PTC was PTC > 10 mm in its maximum diameter. Tumor-node-metastasis (TNM) staging was based on the American Joint Committee on Cancer, 7th edition [16]. Recurrence was defined as new evidence of pathologically proven recurrence in the thyroid bed, soft tissue, cervical LN, or other organs on cytology from aspiration biopsy or reoperation.

Postoperative complications

Fiberoptic laryngoscopy was performed preoperatively and postoperatively in all patients to evaluate the mobility of vocal cord. Transient vocal cord palsy was defined as decreased or absent vocal cord mobility resolving within 6 months of surgery. If vocal cord palsy lasted for more than 6 months, it was considered permanent which confirmed by laryngoscopy. Serum calcium and phosphorus concentrations were measured in all patients after surgery. Transient hypocalcemia was defined as an ionized calcium level < 2.10 mmol/L during the hospital stay and the calcium level recovered normal within 6 months. Permanent hypoparathyroidism was diagnosed in patients still requiring calcium supplementation more than 6 months after surgery. If the patient has postoperative incision bleeding that affected breathing, emergency surgery was performed.

Postoperative management and follow-up

Postoperative suppressive levothyroxine (LT4) treatment was administered to all patients. Thyroid-stimulating hormone (TSH) suppression therapy (serum TSH level below 0.5 mIU/L) with LT4 with or without radioactive iodine (RAI) ablation was used for patients underwent total thyroidectomy. Physical examinations, ultrasonography of the neck and serum thyroglobulin (*T*g) with Tg antibodies were used for all patients every 6 months for 2 years, and annually thereafter. Further imaging examinations or histological confirmation were used when the level of *T*g and/or *T*g antibodies significantly elevated. Follow-up data were obtained by outpatient consultations or telephone contact.

Statistical analyses

All statistical analyzes were carried out using the SPSS v 25.0 software (Chicago, IL, USA). The continuous variables were expressed as the means ± standard deviations (SD). The ^{2} test or Fisher's exact test was used, as appropriate, for categorical data, whereas continuous variables were compared with Student *t* tests or the Manne–Whiney *U* test. Univariate analyzes for the associations between LN metastases and several clinicopathologic factors of the patients were performed using Pearson's chi-square test or Fisher's exact test. Binary logistic regression test was used for multivariate analysis of statistically significant variables from the univariate analysis. Univariate analysis of RFS was realized including each risk factor in a Cox regression model. RFS curves were calculated using the Kaplan–Meier method, and the log-rank test was used to evaluate the differences between curves.

Results

Baseline clinicopathological characteristics of PTC patients

The key clinicopathological characteristics were summarized in Table 1. Our study included 105 men (24.3%) and 327 women (75.7%), with a mean ± SD (Standard Deviation) age of 45.1 ± 12.2 years (range 19–80 years). The mean ± SD size of the primary thyroid tumor was 1.22 ± 0.93 cm (range 0.3–7.5 cm). The extrathyroidal invasion and vascular invasion were seen in 66 and 25 patients, respectively. Multifocality was seen in 118 cases.

LLNM were clinically detected in 61 patients before surgery while 19 patients were suspected of LLNM during surgery, and LND was performed in these patients (18.5%).

The remaining 352 patients (81.5%) underwent CND only. The post-operative examination confirmed that: 206 patients (47.7%) had nodes removed without metastases,161 patients (37.3%) had CLNM only, 55 patients (12.7%) had both CLNM and LLNM, and 10 patients (2.3%) had the skip metastases (LLNM without CLNM). In the central compartment, the mean ± SD number of excised and metastatic LNs was 6.14 ± 4.40 (range 1–31) and 2.42 ± 1.53 (range 0–18), respectively. The mean ± SD number of excised and metastatic lymph nodes in the lateral compartment was 18.75 ± 11.57 (range 0–51) and 4.95 ± 4.75 (range 0–22), respectively.

Tumor stages were as follows: T1 in 218 (50.5%); T2 in 138 (31.9%); T3 in 10 (2.3%); and T4 in 66 (15.3%) patients. Nodal stages were as follows: N0 in 206 (47.7%); N1 in 226 (52.3%) patients. Of 64 PTC patients who were performed BRAF mutation analysis, 56 (87.5%) had BRAF mutation positivity.

Predictors of CLNM

Table 2 shows the association between CLNM and several risk factors in PTC patients. In the univariate analysis, the rate of CLNM was significantly higher in male patients and patients < 45 years of age ($P = 0.033$, $P = 0.004$, respectively). Moreover, tumor size more than 1cm, presence of extrathyroidal invasion, vascular invasion and LLNM were significantly associated with CLNM ($P < 0.001$, $P = 0.002$, $P < 0.001$, respectively). Besides, tumor with higher T

Table 1 Baseline clinicopathological characteristics of 432 PTC patients

Clinicopathological characteristics	No. (%)
Sex	
Male	105 (24.3%)
Female	327 (75.7%)
Age (year)	
Mean ± SD	45.1 ± 12.2
≥ 45	165 (38.2%)
< 45	267 (61.8%)
BMI (kg/m^2)	
Mean ± SD	24.10 ± 3.46
Normal	267 (61.8%)
Overweight	165 (38.2%)
Tumor size (cm)	
Mean ± SD	1.22 ± 0.93
≤ 1	200 (46.3%)
> 1	232 (53.7%)
Multifocality	
Presence	118 (27.3%)
Absence	314 (72.7%)
BRAF mutation[a]	
Presence	56 (87.5%)
Absence	8 (12.5%)
Extrathyroidal invasion	
Presence	66 (15.3%)
Absence	366 (84.7%)
Vascular invasion	
Presence	25 (5.8%)
Absence	407 (94.2%)
Neck dissection	
CND	352 (81.5%)
CND + LND	80 (18.5%)
LNM	
CLNM only	161 (37.3%)
LLNM only	10 (2.3%)
CLNM and LLNM	55 (12.7%)
Absence	206 (47.7%)
Mean no. of removed LNs in the CC (± SD)	6.14 ± 4.40
Mean no. of removed LNs in the LC (± SD)	18.75 ± 11.57
Mean no. of positive LNs in the CC (± SD)	2.42 ± 1.53
Mean no. of positive LNs in the LC (± SD)	4.95 ± 4.75
T classification	
T1	218 (50.5%)
T2	138 (31.9%)
T3	10 (2.3%)
T4	66 (15.3%)
N classification	
N0	206 (47.7%)
N1	226 (52.3%)
TNM staging (7th ed.)	
Stage I	301 (69.7%)
Stage II	37 (8.6%)
Stage III	91 (21.1%)
Stage IV	3 (0.7%)
Recurrence	50 (11.6%)
LN	28 (6.5%)
Thyroid bed	14 (3.2%)
Lung	8 (1.9%)

PTC papillary thyroid carcinoma, *SD* standard deviation, *BMI* body mass index, *CND* central neck dissection, *LND* lateral neck dissection, *LNM* lymph node metastasis, *CLNM* central lymph node metastasis, *LLNM* lateral lymph node metastasis, *LN* lymph node, *CC* central compartment, *LC* lateral compartment

[a]BRAF mutation analysis was started in 2017 and it was performed in 64 patients with PTC

classification and TNM staging were significantly associated with a high prevalence of CLNM (both $P < 0.001$). In the multivariate analysis, patients < 45 years of age (OR 2.037, 95% CI 1.388–2.988, $P < 0.001$), presence of extrathyroidal invasion (OR 2.144, 95% CI 0.824–5.457, $P = 0.011$), presence of vascular invasion (OR 13.817, 95% CI 1.694–112.693, $P = 0.014$), presence of LLNM (OR 2.851, 95% CI 1.196–6.797, $P = 0.014$) and TNM Stage III–IV (OR 465.307, 95% CI 113.903–1900.826, $P < 0.001$) were independent predictors of high prevalence of CLNM.

Predictors of LLNM

Univariate analysis showed that tumor size more than 1cm, presence of extrathyroidal invasion, vascular invasion and CLNM were significantly associated with LLNM ($P < 0.001$, $P = 0.031$, $P < 0.001$, respectively). Moreover, tumor with higher T classification and TNM staging were also significantly associated with a high prevalence of LLNM (both $P < 0.001$) (Table 3). As a result of multivariate analysis, tumor size more than 1cm (OR 3.474, 95% CI 1.728–6.985, $P < 0.001$) and CLNM (OR 5.532, 95% CI 2.679–11.425, $P < 0.001$) were independent predictive factors of LLNM (Table 3).

Postoperative evaluation

As shown in Table 4, 73 of the 352 patients (20.7%) who underwent thyroidectomy and CND developed postoperative complications, which significantly less than those (31.3%) who underwent thyroidectomy combined with CND and LND ($P = 0.043$). Vocal cord paralysis was observed in 53 patients (15.1%) who underwent thyroidectomy and CND. Of these patients, 2 (0.6%) had permanent vocal cord paralysis. For 80 patients who underwent thyroidectomy combined

Table 2 Associations between clinicopathological characteristics and CLNM in PTC patients

Clinicopathological characteristics	CLNM, No. (%)		*P* value	Multivariate analysis	
	Presence ($n=216$)	Absence ($n=216$)		Adjusted OR (95% CI)	*P* value
Sex					
Male	62 (28.7%)	43 (19.9%)	**0.033**	1	
Female	154 (71.3%)	173 (80.1%)		0.602 (0.314–1.153)	0.126
Age (year)					
≥ 45	68 (31.5%)	97 (44.9%)	**0.004**	1	
< 45	145 (68.5%)	119 (55.1%)		2.037 (1.388–2.988)	**< 0.001**
BMI (kg/m^2)					
Normal	135 (62.5%)	132 (61.1%)	0.766		
Overweight	81 (37.5%)	84 (38.9%)			
Tumor size (cm)					
≤ 1	75 (34.7%)	125 (57.9%)	**< 0.001**	1	
> 1	141 (65.3%)	91 (42.1%)		1.662 (0.752–3.675)	0.209
Multifocality					
Unilateral	151 (69.9%)	163 (75.5%)	0.195		
Bilateral	65 (30.1%)	53 (24.5%)			
BRAF mutation[a]					
Absence	34 (89.5%)	22 (84.6%)	0.847		
Presence	4 (10.5%)	4 (15.4%)			
Extrathyroidal invasion					
Absence	163 (75.5%)	203 (94.0%)	**< 0.001**	1	
Presence	53 (24.5%)	13 (6.0%)		2.144 (0.842–5.457)	**0.011**
Vascular invasion					
Absence	196 (90.7%)	211 (97.7%)	**0.002**	1	
Presence	20 (9.3%)	5 (2.3%)		13.817 (1.694–112.693)	**0.014**
LLNM					
Absence	161 (74.5%)	206 (95.4%)	**< 0.001**	1	
Presence	55 (25.5%)	10 (4.6%)		2.851 (1.196–6.797)	**0.018**
T classification					
T1–T2	159 (73.6%)	197 (91.2%)	**< 0.001**	1	
T3–T4	57 (26.4%)	19 (8.8%)		1.571 (0.682–3.616)	0.289
TNM staging (7th ed.)					
Stage I–II	128 (59.3%)	210 (97.2%)	**< 0.001**	1	
Stage III–IV	88 (40.8%)	6 (2.8%)		465.307 (113.903–1900.826)	**< 0.001**

Bold indicates $P < 0.05$ and has statistical significance

PTC papillary thyroid carcinoma, *BMI* body mass index, *CLNM* central lymph node metastasis, *LLNM* lateral lymph node metastasis, *OR* Odds ratio, *95% CI* 95% confidence interval

[a]BRAF mutation analysis was started in 2017 and it was performed in 64 patients with PTC

with CND and LND, 20 (25.0%) developed vocal cord paralysis, and 5 (6.3%) had had permanent vocal cord paralysis. In patients who underwent thyroidectomy and CND, 13 (3.7%) developed postoperative hypocalcemia requiring calcium supplement, and 3 (0.9%) had permanent hypocalcemia requiring calcium supplement for more than 6 months after surgery. While 9 of 80 patients (11.3%) who underwent thyroidectomy combined with CND and LND had postoperative hypocalcemia, and 6 (7.5%) developed permanent hypocalcemia. Three patients (0.9%) who underwent thyroidectomy and CND required emergency surgery due to immediate postoperative bleeding, which significantly less than the patients (5.0%) who underwent thyroidectomy combined with CND and LND. There were no postoperative deaths.

Follow-up and recurrences

Postoperative follow-up ranged from 6 to 89 months (average follow-up period: 42 months). During follow-up, 50 patients (11.6%) developed recurrent disease, including 28

Table 3 Associations between clinicopathological characteristics and LLNM in PTC patients

Clinicopathological characteristics	LLNM, No. (%)		*P* value	Multivariate analysis	
	Presence ($n=65$)	Absence ($n=367$)		Adjusted OR (95% CI)	*P* value
Sex					
Male	18 (27.7%)	87 (23.7%)	0.490		
Female	47 (72.3%)	280 (76.3%)			
Age (year)					
≥ 45	27 (41.5%)	185 (50.4%)	0.187		
< 45	38 (58.5%)	182 (49.6%)			
BMI (kg/m^2)					
Normal	38 (58.5%)	229 (62.4%)	0.547		
Overweight	27 (41.5%)	138 (37.6%)			
Tumor size (cm)					
≤ 1	12 (18.5%)	188 (51.2%)	**< 0.001**	1	
> 1	53 (81.5%)	179 (48.8%)		3.474 (1.728–6.985)	**< 0.001**
Multifocality					
Unilateral	43 (66.2%)	271 (73.8%)	0.200		
Bilateral	22 (33.8%)	96 (26.2%)			
BRAF mutation[a]					
Absence	2 (13.3%)	6 (12.2%)	1.000		
Presence	13 (86.7%)	43 (87.8%)			
Extrathyroidal invasion					
Absence	44 (67.7%)	322 (87.7%)	**< 0.001**	1	
Presence	21 (32.3%)	45 (12.3%)		1.791 (0.904–3.550)	0.095
Vascular invasion					
Absence	57 (87.7%)	350 (95.4%)	**0.031**	1	
Presence	8 (12.3%)	17 (4.6%)		1.185 (0.365–3.851)	0.777
CLNM					
Absence	10 (15.4%)	206 (56.1%)	**< 0.001**	1	
Presence	55 (84.6%)	161 (43.9%)		5.532 (2.679–11.425)	**< 0.001**
T classification					
T1–T2	43 (66.2%)	313 (85.3%)	**< 0.001**	1	
T3–T4	22 (33.8%)	54 (14.7%)		1.660 (0.192–14.380)	0.645
TNM staging (7th ed.)					
Stage I–II	38 (58.5%)	300 (81.7%)	**< 0.001**	1	
Stage III–IV	27 (41.5%)	67 (18.3%)		1.412 (0.743–2.683)	0.293

Bold indicates $P < 0.05$ and has statistical significance

PTC papillary thyroid carcinoma, *BMI* body mass index, *LLNM* lateral lymph node metastasis, *CLNM* central lymph node metastasis, *OR* Odds ratio, *95% CI* 95% confidence interval

[a]BRAF mutation analysis was started in 2017 and it was performed in 64 patients with PTC

patients (6.5%) had cervical lymph nodes recurrence, 14 patients (3.2%) had thyroid bed recurrence and 8 patients (1.9%) had lung recurrence (Table 1). The rate of recurrence in patients with CLNM was 16.2%, which was significantly higher than 6.9% in patients without CLNM ($P=0.003$). The prevalence of LNs recurrence was significantly higher in patients with CLNM than patients without CLNM (9.7%, 3.2%, respectively, $P=0.006$). Despite the rate of recurrence in patients with LLNM was higher than patients without LLNM (18.5%, 10.4%, respectively), there was no statistical difference ($P=0.060$) (Table 5).

Predictors of RFS

Univariate analyzes in relation to RFS was conducted to determine the single variable which influenced risk of recurrence (Table 6). Tumor with T3–T4 stage, presence of extrathyroidal invasion and CLNM were the significant

Table 4 Association between postoperative complications and operation in PTC patients

Clinicopathological characteristics	Operation, No. (%)		*P* value
	Thyroidectomy + CND ($n = 352$)	Thyroidectomy + CND + LND ($n = 80$)	
Postoperative complications[a]	73 (20.7%)	25 (31.3%)	**0.043**
Vocal cord palsy	53 (15.1%)	20 (25.0%)	**0.032**
Transient	51 (14.5%)	15(18.8%)	0.339
Permanent	2 (0.6%)	5 (6.3%)	**0.002**
Hypocalcaemia	13 (3.7%)	9 (11.3%)	**0.013**
Transient	10 (2.8%)	3 (3.8%)	0.946
Permanent	3 (0.9%)	6 (7.5%)	**0.001**
Incision infection	6 (1.7%)	4 (5.0%)	0.175
Bleeding required resurgery	3 (0.9%)	4 (5.0%)	**0.031**

Bold indicates $P < 0.05$ and has statistical significance

PTC papillary thyroid carcinoma, *CND* central neck dissection, *LND* lateral neck dissection

[a]More than one complication occurred in some patients

Table 5 Association between postoperative recurrence and CLNM/ LLNM in PTC patients

Clinicopathological characteristics	CLNM, No. (%)		*P* value	LLNM, No. (%)		*P* value
	Presence ($n = 216$)	Absence ($n = 216$)		Presence ($n = 65$)	Absence ($n = 367$)	
Postoperative recurrence	35 (16.2%)	15 (6.9%)	**0.003**	12 (18.5%)	38 (10.4%)	0.060
LN	21 (9.7%)	7 (3.2%)	**0.006**	7 (10.8%)	21 (5.7%)	0.211
Thyroid bed	9 (4.2%)	5 (2.3%)	0.277	3 (4.6%)	11 (3.0%)	0.765
Lung	5 (2.3%)	3 (1.4%)	0.721	2 (3.1%)	6 (1.6%)	0.767

Bold indicates $P < 0.05$ and has statistical significance

PTC papillary thyroid carcinoma, *CLNM* central lymph node metastasis, *LLNM* lateral lymph node metastasis, *LN* lymph node

factors related to the RFS ($P < 0.001$, $P < 0.001$, $P = 0.012$, respectively), while other investigated variables had no influence on RFS. Patients with extrathyroidal invasion had 3.945 times higher risk of recurrence than patients without extrathyroidal invasion (Table 6 and Fig. 2). Patients with CLNM had 3.120 times higher risk of recurrence than patients without CLNM (Table 6 and Fig. 3). Similarly, risk of recurrence was 3.394 times higher among patients with T3–T4 stage (Table 6 and Fig. 4).

Discussion

Several studies have confirmed the metastatic lymph node size, number and ratio may have influence on locoregional recurrence in patients with PTC [17, 18, 19]. However, the association between LNM and primary tumor characteristics has not been fully established. Prophylactic lymph node dissection has the potential to reduce recurrence and survival, but may lead to clinically important postoperative morbidity [12, 13]. Hence, the associations between primary tumor characteristics and LNM were analyzed to improve the individualized treatment and to avoid the unnecessary prophylactic lymph node dissection.

The prevalence of overall LNM in this study was 52.3%, including 37.3% in CLNM, 12.7% in CLNM and LLNM, and 2.3% in the skip metastases, which conforms to incidence of LNM previously reported [3, 4, 5]. In the present study, the LNM pattern according to neck level was similar to that reported previously [20]. Cervical LNM occurs first at the node of the central compartment and then at the node of the lateral compartment, while the skipping metastasis is rare. Considering the fact that reoperation for recurrence of the central compartment may cause significant complications such as recurrent laryngeal nerve damage and persistent hypoparathyroidism, Japanese Society of Thyroid Surgeons (JSTS) recommend to routinely perform the prophylactic CND [21]. Although we did not conduct prospective studies to demonstrate whether conventional prophylactic CND could improve prognosis, we found that CLNM is a poor prognostic factor for PTC patients. Patients with CLNM had 3.12 times higher risk of recurrence than patients without CLNM. In addition, in a subgroup analysis, we found that patients with CLNM

Table 6 Cox proportional hazards model demonstrating factors associated with recurrence–free survival in patients with PTC

Clinicopathological characteristics	HR	95% CI	*P* value
Sex			
Male	1		
Female	1.226	0.655–2.295	0.524
Age (year)			
< 45	1		
≥ 45	0.605	0.232–1.579	0.304
BMI (kg/m^2)			
Normal	1		
Overweight	1.714	0.918–3.199	0.091
Tumor size (cm)			
≤ 1	1		
> 1	1.072	0.561–2.047	0.833
Multifocality			
Unilateral	1		
Bilateral	1.421	0.691–2.923	0.339
Extrathyroidal invasion			
Absence	1		
Presence	3.945	2.260–6.884	**< 0.001**
Vascular invasion			
Absence	1		
Presence	1.866	0.947–3.675	0.071
CLNM			
Absence	1		
Presence	3.120	1.288–7.560	**0.012**
LLNM			
Absence	1		
Presence	1.288	0.742–2.236	0.368
T classification			
T1–T2	1		
T3–T4	3.394	1.945–5.924	**< 0.001**
TNM staging (7th ed.)			
Stage I–II	1		
Stage III–IV	1.541	0.564–4.205	0.399

Bold indicates $P < 0.05$ and has statistical significance

PTC papillary thyroid carcinoma, *BMI* body mass index, *CLNM* central lymph node metastasis, *LLNM* lateral lymph node metastasis, *HR* Hazard ratio, *95% CI* 95% confidence interval

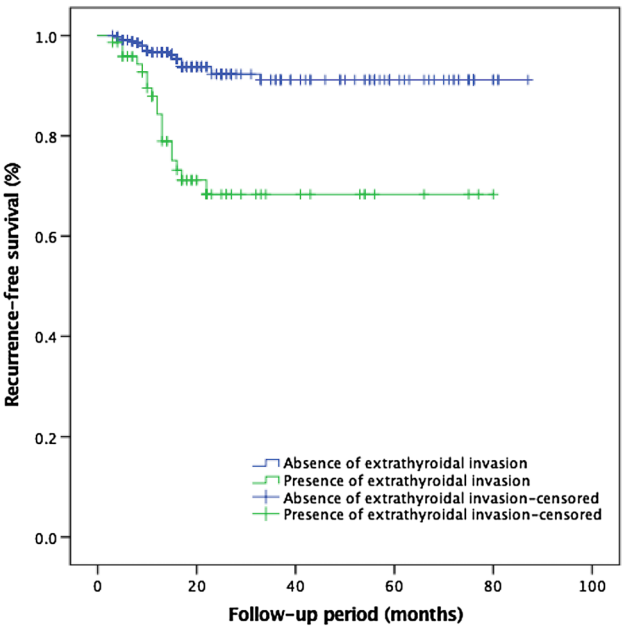

Fig. 2 Recurrence–free survival by presence or absence of extrathyroidal invasion in patients with PTC

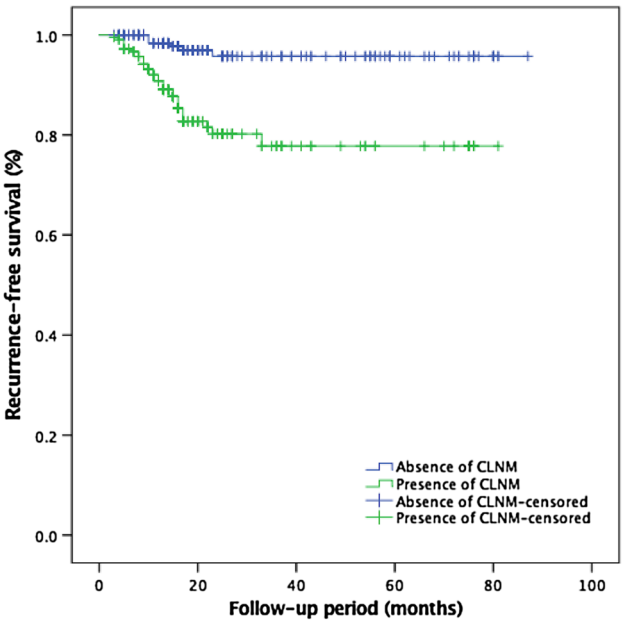

Fig. 3 Recurrence–free survival by presence or absence of central lymph node metastasis in patients with PTC

are prone to recurrence in cervical LNs. Yuan et al. [22] suggested that risk factors affecting CLNM were less than 45 years old, greater than 2cm of tumor size and bilaterality, while the effect of extrathyroidal invasion and vascular invasion had no significant difference. Koo et al. [23] considered that risk factors affecting CLNM were age, thyroid capsule invasion, greater than 1 cm of tumor size and lymphatic invasion. In this study, we found that patients aged less than 45 years, presence of extrathyroidal invasion, presence of vascular invasion, presence of LLNM, or having TNM stage III–IV, would have a high prevalence of CLNM. A part of these risk factors could be pre-operatively identified with US. For example, extrathyroidal invasion could be detected by pre-operative US with a sensitivity of 78.5–80.1% [24]. Besides, massive extrathyroidal invasion could be also detected intraoperatively. Considering the low sensitivity (51–58.3% only) of

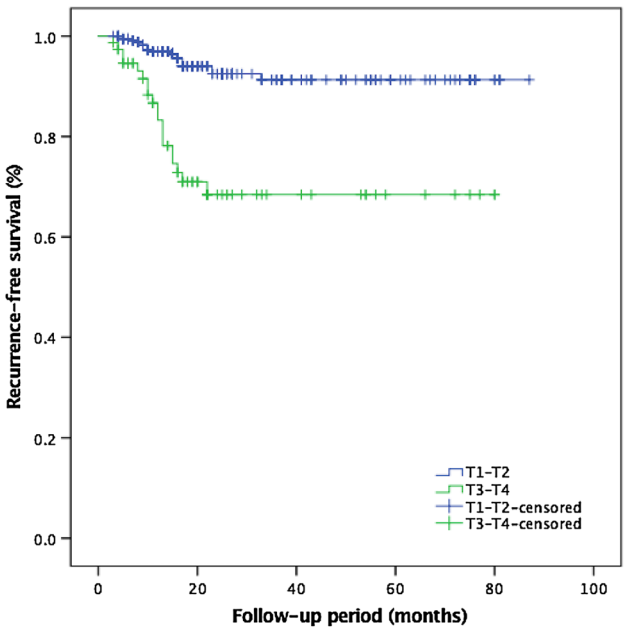

Fig. 4 Recurrence–free survival by T classification in patients with PTC

neck US for detecting LNM in central compartment [25, 26], we conclude that careful prophylactic CND should be recommended for PTC patients with above risk factors.

Although the second most common compartment for LNM is the lateral neck, none of the leading guidelines recommended prophylactic LND, moreover, the indication for prophylactic LND remained controversial [10, 11, 21]. In our study, we showed that the incidence of LLNM increased with the tumor size and presence of CLNM. On the contrary, the presence of LNM in lateral compartment does not increase the risk of recurrence of PTC in a series of cN0 or cN1 patients. Compared with patients without LLNM, patients with LLNM had higher risk of recurrence in cervical LNs, thyroid bed and lung, but there was no statistical difference, which was consistent with the result of Nobuyuki et al. [27] that patients undergoing prophylactic LND had the same recurrence rate as those who did not. This may attribute to the lymphatic drainage characteristics of central compartment, which was broader and multidirectional than lateral compartment [28]. From the perspective of quality of postoperative life, LND, especially level V lymphadenectomy, may lead to postoperative morbidity associated with the spinal accessory nerve and postoperative dysfunction in the strength of the trapezius muscle secondary to traction, devascularization, or thermal injury. Moreover, patients who underwent LND had a higher prevalence of permanent vocal cord palsy, permanent hypocalcaemia and emergency surgery than those with CND only. Therefore, from the perspective of postoperative recurrence, survival and quality of life, we recommend to perform LND only for patients with LLNM instead of performing prophylactic LND for high risk patients without LLNM.

Various factors and the staging system have been used to predict the prognosis in patients with PTC. Age, tumor size, extrathyroidal invasion, and neck LNM were generally accepted variables that were related to survival and recurrence [29, 30, 31]. In our data, apart from the CLNM, presence of extrathyroidal invasion and tumor with T3–T4 stage were significantly associated with RFS. It was not surprising to identify association between T classification and RFS. The risk of recurrence in patients with extrathyroidal invasion was 3.945 times higher than that in patients without extrathyroidal invasion. Similarly, many authors also found that patients with extrathyroidal invasion seemed to have higher mortality and recurrence rates than those without. Arora t al. [29] presumed that the extrathyroidal invasion itself had a negative effect on survival, while Clain et al. [30] and Noguchi et al. [31] showed that extrathyroidal invasion was associated with extranodal extension in LNM and had an effect on the survival rate. In our study, patients with extrathyroidal invasion were 2.144 times more likely to have CLNM than those without extrathyroidal invasion. The association between extrathyroidal invasion and CLNM may provide a theoretical basis for managing LNs in patients with PTC.

There are several potential limitations in our study. First, our study cohort was a retrospective study, and all data were collected from a single medical center, features of a nonrandomized would be produced inevitably. Second, we lacked information on other exposures, the possibility of residual confounding variables of measured or unmeasured factors were not ruled out. Third, different surgeons participated in the management of patients, there may have be differences in performing thyroidectomy or lymph node dissection.

In conclusion, our study demonstrated that age, extrathyroidal invasion, vascular invasion, LLNM and TNM stage were the important predictive factors for CLNM in PTC patients, while tumor size and CLNM were the predictive factors for LLNM. Therefore, for patients with pre–operative risk factors of LNM, an accurate preoperative evaluation of central compartment or lateral compartment is needed to find suspicious LNs. And prophylactic CND should be performed in patients with high risk of CLNM. Moreover, CLNM, extrathyroidal invasion and T classification were significantly associated with RFS. We suggest performing close follow-up for patients with high risk of RFS.

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Compliance with ethical standards

Conflict of interest This manuscript has not been published nor submitted for publication elsewhere. All authors have contributed significantly, and agree with the content of the manuscript. The authors reported no proprietary or commercial interest in any product mentioned or concept discussed in this article.

Ethical approval This study has been approved by the Institutional Review Board of Changzhou First People's Hospital ethics committee, and has been performed according to the ethical standards laid down in the 1964 Declaration of Helsinki.

Informed consent Informed consent was obtained from all individual participants included in the study.

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