

Clinicopathological features for predicting central and lateral lymph node metastasis in papillary thyroid microcarcinoma: Analysis of 66 cases that underwent central and lateral lymph node dissection

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Abstract. Currently the surgical approach for papillary thyroid microcarcinoma (PTMC), particularly the range of lymph node dissection, remains controversial. The present study aims to evaluate the risk factors for central and lateral lymph node metastasis (CLNM and LLNM) for appropriate clinical decision of neck lymph node dissection in PTMC. A total of 66 cases of PTMC that underwent unilateral or bilateral lobectomy plus prophylactic cervical lymph node dissection were collected for clinicopathological evaluation, including age, gender, tumor size, subtypes, extrathyroidal invasion, multifocality, calcifications, loss of cellular polarity/cohesiveness (LOP/C) in the invasive front, CLNM and LLNM, and retrospectively analysis. Univariate analysis revealed that LOP/C was significantly associated with CLNM ($P=0.001$) and LLNM ($P<0.0001$). The male gender was a risk factor of CLNM ($P=0.04$), while the age <45 years, tumor size >0.5 cm and multifocality were high-risk factors of LLNM ($P=0.022$, 0.044 and 0.005 , respectively). Multivariable analysis revealed that LOP/C was significantly associated with CLNM [$P=0.007$, odds ratio (OR)=7.765, 95% confidence interval (CI)=1.773-33.996] and LLNM [$P=0.029$, OR=5.717, 95% CI=1.190-27.470]. Both multivariable analysis and χ^2 test revealed that CLNM was another important high-risk factor of LLNM ($P=0.021$, OR=5.444, 95% CI=1.290-22.969, $\chi^2=17.867$,

$P<0.001$). The present study revealed that prophylactic central lymph node dissection is essential for PTMC surgery and that prophylactic lateral lymph node dissection is recommend for patients with LOP/C and CLNM, which can be performed by intraoperative frozen section pathological examination. This must be considered discreetly in the case of patients with age <45 years, tumor size >0.5 cm and multifocal lesions.

Introduction

The annual incidence of thyroid carcinoma is 6.2% (1) and accounts for 2.7% of all malignant tumor types in females worldwide (2,3). Papillary thyroid microcarcinoma (PTMC), which is defined as a papillary carcinoma with the dimensions equal to or <1.0 cm, according to the World Health Organization classification (4), accounts for 6-35% of thyroid carcinoma and 35.7-61.5% of papillary thyroid carcinoma (PTC) (5-10). PTMC is considered with favorable biological features and good long-term prognosis, as the 10-year disease-specific survival of 99.5% (11). The rate of neck lymph metastasis is 3.1-45.7%, and the sites include level II, III, IV, V, VI (12-14). Lymph node metastasis, particularly central lymph node metastasis (CLNM), is considered to be the most important risk factor associated with recurrence (15-17).

Currently, the surgical approach for PTMC, particularly the ranges of lymph nodes dissection remains controversial (18,19). Although numerous previous studies have suggested that unilateral or bilateral lobectomy, plus prophylactic central lymph node dissection (PCLND; dissection of the level VI lymph nodes which lie in central position of the neck (6,20), including prelaryngeal, pretracheal and paratracheal lymph nodes) for PTMC is enough (21-23), and even overtreatment is performed when no positive lymph nodes were identified in clinical examination (cN0), others still insist that prophylactic lateral lymph node dissection (PLLND) should be performed in certain conditions (24,25). PCLND may cause temporary parathyroid laryngeal damage and injury to laryngeal

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nerves (26); PLLND may damage accessory nerves, cervical plexus and cause additional complications. Neck ultrasound (US) and contrast-enhanced computed tomography (CT) are widely used for preoperative imaging to visualize the lymph metastasis; unfortunately, both US and contrast-enhanced CT are not particularly accurate, with low sensitivities of 23-53.2 and 41-66.7%, respectively (27,28). Therefore, the risk factors of CLNM and LLNM are important for surgeons to determine the range of neck lymph dissection. Current research demonstrated that age ≥ 45 years, tumor size >0.5 cm, extrathyroid invasion, multifocality and calcifications were all possible risk factors of CLNM (13,16-20); however, few previous studies have investigated predicting factors of LLNM.

Loss of cellular polarity/cohesiveness (LOP/C) in the invasive front was considered to be a useful morphological feature of the epithelial-mesenchymal transition (EMT) under hematoxylin and eosin staining (29). LOP refers to a phenomenon in which the carcinoma cells are arranged in micropapillary structures with a fibrous axis or irregular tubular patterns, and the nuclei were round and located in the apical cytoplasm, or flat and located centrally (30-32). LOC means that the carcinoma cells were loosely arranged, singly or in small clusters resembling foamy histiocytes or in micropapillary structures (29-32). The invasive front was defined as the interface between the tumor and the adjacent non-neoplastic tissue when the tumor exhibited invasive growth, in which desmoplasia is usually observed (29-32). When LOP/C was definitely present in at least two sites in the invasive front, it is considered to be significant (30). In PTC, LOP/C is associated with increased risk of lymph node metastasis, extrathyroid invasion and aggressive clinical behavior (29); however, the role of LOP/C in PTMC remains to be investigated. In the present study, LOP/C in PTMC was observed and analyzed.

Materials and methods

Patients. The clinical data of 66 patients with PTMC, who underwent unilateral or bilateral lobectomy plus prophylactic cervical lymph node dissections between January 2008 and June 2015 in the Affiliated Hospital of Shandong Medical Sciences (Shandong, China) were retrospectively analyzed. All cases were unilateral lesion and cervical lymph node cN0. The age range was 19-69 years (median, 43.5 years) and the ratio of male:female was 1:4.08. All PTMC patients were confirmed by intraoperative frozen section pathological examination, followed by unilateral or bilateral lobectomy and prophylactic ipsilateral regional lymphadenectomy, including level II, III, IV, V, VI, were performed. Postoperative paraffin section histopathology examinations were performed and pathological features, including subtypes, tumor size, extrathyroidal invasion, multifocality, calcifications, LOP/C, CLNM and LLNM were subjected to a meticulous histopathology examination by two pathologists (Zhiyan Liu and Xiangshan Yang).

Statistical analysis. Fisher's exact test or χ^2 test, and binary logistic regression were used to investigate the cases using SPSS software (version 17.0; SPSS, Inc., Chicago, IL, USA). $P < 0.05$ was considered to indicate a statistically significant difference.

Table I. Neck lymph metastasis of 66 papillary thyroid microcarcinoma cases.

Neck lymph node stage	Neck lymph node metastasis	
	Positive, n (%)	Negative, n (%)
II	11 (20.0)	55 (80.0)
III	20 (30.3)	46 (69.7)
IV	17 (25.8)	49 (74.2)
V	3 (4.8)	63 (95.2)
VI	37 (56.1)	29 (43.9)

Results

Neck lymph metastasis of 66 PTMC cases. A total of 60.6% (44/66) of cases exhibited neck lymph metastasis, including central and lateral. Only 36.4% (24/66) cases exhibited CLNM and LLNM simultaneously, 13.6% (10/66) have CLNM without LLNM and 9.1% (6/66) have LLNM only. The lymph node metastasis rate of level II, III, IV demonstrated no statistical significance (20, 30.3 and 25.8, respectively, $\chi^2=3.465$, $P=0.177$). Compared with these groups, level VI was higher with a rate of 56.1% (37/66, $\chi^2=25.871$, $P < 0.0001$) and level V was lower (4.8%, 3/66, $\chi^2=16.404$, $P < 0.01$) (Table I).

Univariate analysis outcome of the high-risk factors of total neck lymph metastasis of PTMC. Univariate analysis revealed that LOP/C was significantly associated with both central or lateral lymph metastasis ($P=0.001$ and $P < 0.0001$), and the male gender exhibited a statistical significant difference compared with female in CLNM (76.9 vs. 45.3%, $P=0.04$), while the age < 45 years, tumor size > 0.5 cm and multifocality were high-risk factors of LLNM ($P=0.022$, 0.044 and 0.005, respectively). Extrathyroid invasion and calcifications were demonstrated to be not statistically significant with CLNM and LLNM (Table II).

The data of binary logistic regression for outcome of the central and lateral lymph metastasis risk factors of PTMC revealed that LOP/C was significantly associated with CLNM ($P=0.007$) and LLNM ($P=0.029$) (Tables III and IV). Both multivariable analysis and χ^2 test revealed that CLNM was another important risk factor of LLNM ($P=0.021$; Table IV) ($\chi^2=17.867$, $P < 0.001$, Table V). Gender, age, subtypes, extrathyroid invasion, multifocality and calcifications failed to reach statistical significance for either CLNM or LLNM (Tables III and IV).

Discussion

The male gender and an age ≥ 45 have been consistently recognized as independent risk factors of lymph metastasis in thyroid carcinoma (33). However, in PTMC, this view is remains controversial. The result of Zhao *et al* (34) shows male gender and age ≥ 45 are at a higher risk of lymph node metastasis; however, certain other previous studies demonstrated that no statistically significant association existed between

Table II. Univariate analysis of papillary thyroid microcarcinoma total neck lymph metastasis.

Risk factor	Cases, n	Central lymph node metastasis, n (%)	P-value	Lateral lymph node metastasis, n (%)	P-value
Gender					
Male	13	10 (76.9)	0.040 ^a	8 (61.5)	0.086
Female	53	24 (45.3)		19 (35.8)	
Age, years					
≥45	33	14 (47.4)	0.109	9 (27.3)	0.022 ^a
<45	33	20 (60.6)		18 (54.5)	
Tumor size					
≤0.5 cm	34	15 (44.1)	0.160	10 (29.4)	0.044 ^a
>0.5 cm	32	19 (59.4)		17 (53.1)	
Subtypes					
CPV	31	18 (58.1)	0.788	15 (48.4)	0.643
UCPV	17	8 (47.1)		7 (41.2)	
FCV	10	4 (40.0)		2 (20.0)	
TCV	5	3 (60.0)		2 (40.0)	
DSV	3	1 (33.3)		1 (33.3)	
Extrathyroid invasion					
Yes	27	13 (48.1)	0.419	10 (37.0)	0.392
No	39	21 (53.8)		17 (43.9)	
Multifocality					
Yes	38	22 (57.9)	0.169	21 (55.3)	0.005 ^a
No	28	12 (42.9)		6 (21.4)	
Calcifications					
Yes	10	6 (66.7)	0.269	6 (66.7)	0.093
No	56	28 (49.1)		21 (36.8)	
LOP/C					
Yes	23	18 (78.3)	0.001 ^a	17 (73.9) ^b	0.0001 ^a
No	43	16 (37.2)		10 (23.3)	

^aP<0.05; ^bThe rate of LLNM was 83.3% (15/18) when LOP/C and CLNM existed simultaneously. CPV, classical papillary variant; UCPV, unclassical papillary variant; FCV, follicular variant; TCV, tall cell variant; DSV, diffuse sclerosing variant; LOP/C, loss of cellular polarity/cohesiveness; LLNM, lateral lymph node metastasis; CLNM, central lymph node metastasis.

them (20,34,35). The research of 1,990 PTMC cases reported that the male incidence of thyroid carcinoma was associated with absence of environment protection mechanisms and emphasized that surgical intervention may possibly improve male's prognosis (36). An age ≥45 is commonly considered as a risk factor for tumor recurrence and lymph node metastasis, however, other literature has suggested that adolescents tend to develop neck lymph node metastasis (35-37). The univariate analysis revealed that male gender tended to associate more with CLNM (10/13, 76.9%, P=0.04) and patients <45 years were more at risk of LLNM (18/33, 54.5%, P=0.022). However, in the multivariate analysis, these factors failed to reach statistical significance (Tables III and IV).

Tumor size >0.5 cm is also recognized as a risk factor for lymph node metastasis in PTMC (17,35). PTMC with size >0.5 cm may be associated with more vascular and extrathyroid invasion, more incidence in females and more CLNM (38). Lee *et al* (39) demonstrated that PTMC CLNM of

tumor size ≤0.5 cm compared with size >0.5 cm was 18.2 vs. 29.2% (P=0.018), and LLNM was only 5.5% (39). The present univariate analysis results revealed more LLNM of PTMC >0.5 cm (53.1 vs. 29.4%, P=0.044); however, it still failed to reach statistical significance in the multivariate analysis.

A total of 5 subtypes were found in the 66 cases, according to pathological features (40): Classical papillary variant (CPV), unclassical papillary variant (UCPV), follicular variant (FCV), tall cell variant (TCV) and diffuse sclerosing variant (DSV). TCV and DSV were considered as aggressive variants (41) and tend to exhibit more aggressive pathological characteristics, including higher rates of extrathyroidal extension compared with classic PTMC, more multifocality in TCV and more lymph metastasis in DSV; however, the survival appears to be similar (42). In the present study, CLNM and LLNM exhibited no statistically significant difference between each subtype, and subtype was not a high risk factor of CLNM and LLNM (P=0.251 and 0.381, respectively; Tables III and IV). However,

Table III. Multivariable analysis of risk factors for papillary thyroid microcarcinoma central lymph node metastasis.

Risk factor	Partial regression coefficient B	SE	Wald	DOF	P-value	OR
Age	0.330	0.050	0.425	1	0.515	1.033
Gender	1.698	0.941	3.256	1	0.071	5.461
Tumor size	-0.306	1.058	0.084	1	0.772	0.736
Subtype	0.227	0.260	0.768	1	0.381	1.225
Extrathyroid invasion	-0.224	0.669	0.133	1	0.716	0.784
Multifocality	-0.950	0.828	1.315	1	0.251	0.387
Calcifications	1.671	1.095	2.329	1	0.127	5.316
LOP/C	2.050	0.753	7.401	1	0.007 ^a	7.765

^aP<0.01; OR=7.765; 95% confidence interval=1.773-33.996. LOP/C, loss of cellular polarity/cohesiveness; SE, standard error; DOF, degrees of freedom; OR, odds ratio.

Table IV. Multivariable analysis of risk factors for papillary thyroid microcarcinoma lateral lymph node metastasis.

Risk factor	Partial regression coefficient B	SE	Wald	DOF	P-value	OR
Age	0.007	0.060	0.014	1	0.906	1.007
Gender	0.353	1.062	0.111	1	0.739	1.424
Tumor size	-0.773	1.373	0.317	1	0.573	0.462
Subtype	0.270	0.336	0.647	1	0.421	1.311
Extrathyroid invasion	-1.017	0.847	1.440	1	0.230	0.362
Multifocality	-0.910	1.020	0.796	1	0.372	2.485
Calcifications	1.020	1.166	0.766	1	0.382	2.774
LOP/C	1.743	0.801	4.739	1	0.029 ^a	5.717
CLNM	1.694	0.735	5.321	1	0.021 ^b	5.444

^aP<0.05, OR=5.717, 95% confidence interval=1.190-27.470; ^bP<0.05, odds ratio=5.444, 95% CI (1.290~22.969). LOP/C, loss of cellular polarity/cohesiveness; SE, standard error; DOF, degrees of freedom; CLNM, central lymph node metastasis; OR, odds ratio.

Table V. Association between central lymph node metastasis and lateral lymph node metastasis.

Central lymph node metastasis	n	Lateral lymph node metastasis, n (%)		χ^2
		Positive	Negative	
Positive	34	24 (70.6)	10 (29.4)	17.867 ^a
Negative	32	6 (18.8)	23 (81.2)	

^aP<0.001.

due to a reduced number of DSV and TSV, further research is required.

Extrathyroid invasion, multifocality and calcification are all valuable high-risk factors of lymph metastasis of PTMC (43-45). PTMC with these pathological characters exhibit more aggressive biological behavior (42). Multifocality was considered the intraglandular spread of the primary tumor, which indicated the tumor cells were apt to shed off

from primary lesion and distribute in thyroid (46,47). When the primary lesion penetrated the fibrous capsule of thyroid, the tumor cells metastasized easier without the restrain of the capsule (29). Shindo *et al* (44) and Chow *et al* (48) reported that neck lymph node metastasis was significantly correlated with tumor multifocality. Multiple microcalcifications were recognized as an important feature of malignancy, and PTMC with calcification was detected with a large size and higher

lymph node ratio compared with non-calcified lesions (45). Unfortunately, these options remain controversial (34,38). The present univariate analysis result revealed that multifocality was a significant high-risk factor for LLNM, however, in the multivariate analysis, they were not significant.

The EMT is a crucial step in the process of migration of carcinoma tumors from the primary site into surrounding tissues (49-51), which features a loss of epithelial properties and the acquisition of mesenchymal properties, including the loss of apical-basal polarity, loss of cell-cell adhesion, loss of E-cadherin expression, and overexpression of vimentin, epidermal growth factor receptor (EGFR), matrix metalloproteinase-9, TGF- β , NF κ B and integrin pathway members in the invasive front (52,53). However, the affirmation of the EMT requires examination of biomarkers, including E-cadherin, N-cadherin, vimentin and fibronectin (53,54). LOP/C in the invasive front is considered to be a useful morphological feature of the EMT, and can be observed directly under hematoxylin and eosin staining, without immunohistochemical examination (29). PTCs with LOP/C was significantly correlated with poor clinical outcome as extrathyroid invasion and lymph node metastasis more frequently, and the majority exhibited extrathyroid invasion and were in an advanced tumor stage at surgery (29-32). The present research revealed that in PTMC, more multifocality (20/23 vs. 18/43, $\chi^2=12.476$, $P<0.0001$), CLNM and LLNM were more observed in the cases with LOP/C compared with the cases without (Table II), which proved that the invasive capacity of tumor was enhanced, and LOP/C was confirmed to be a high-risk factor of CLNM and LLNM ($P=0.007$ and 0.029 , respectively; Tables III and IV).

PCLND is recommended as the standard treatment of PTMC; however, the controversy has never ceased. Certain surgeons advocate that PCLND must not be recommended to patients with PTMC, for its reduced malignancy, and PCLND may cause perioperative side effect, including hypoparathyroidism and laryngeal nerve injury (55,56). Additionally, CLNM does not affect the PTMC prognosis (57), even with re-operation following recurrence (58). By contrast, other clinicians suggest that PCLND can reduce the recurrence and improve the survival (59,60). Previous research has revealed that CLNM of PTMC, without risk factors such as male gender, age ≥ 45 , extrathyroid invasion, multifocality and aggressive subtype, was only 6.80-8.13% and PCLND was not recommend (20,36). On the contrary, PCLND was necessary in PTMC with these factors (13,25). However, in the present study, the high risk factors of CLNM were male gender and LOP/C (Tables III and IV). A total of 56.1% (37/66) of patients exhibited CLNM, while the rate of CLNM with male gender and LOP/C was 87.0% (20/23) compared with 32.5% (14/43) in patients without these factors ($\chi^2=10.267$, $P<0.001$). These data indicate that PCLND may be necessary for PTMC, regardless of the high risk factors.

PLLND of PTMC has not been emphasized due to of the low incidence of LLNM; for example, 5.5% (39) and less effect on the survival (23). However, Zeng *et al* (25) found that the rate of LLNM was 30.5% (43/141) and the number of positive central lymph node ≥ 2 , accompanying with Hashimoto's thyroiditis and extrathyroidal extension were the independent predictive factors for LLNM (25). Another analysis revealed that the presence of CLNM, upper third location of malignancy and tumor size were independent factors for predicting LLNM (61). The present result demonstrated that 45.5% (30/66) cases exhibited LLNM and the ratio of II, III, IV, V was 20, 30.3, 25.8 and 4.8%, respectively. A total of 70.6% (24/34) of the cases with CLNM had LLNM and it was significantly higher compared with the 18.8% (6/32) of the cases without CLNM ($\chi^2=17.867$, $P<0.001$; Table V), and the ratio was 81.8% (18/22) when the number of CLNM ≥ 2 . CLNM and LOP/C were high-risk factors of LLNM in both univariate and multivariate analyses; The rate of LLNM was 83.3% (15/18) when LOP/C and CLNM existed simultaneously. An age <45 years, tumor size >0.5 cm and multifocality were significant in the univariate analysis. The rate of LLND in PTMC without age <45 years, tumor size >0.5 cm, multifocality, LOP/C and CLNM was 0% (0/9). In the factors mentioned above, CLNM and LOP/C were important and useful since intraoperative frozen section pathological examination can confirm them and assist the surgeon to make the decision whether PLLND should be performed, even though no evidence suggests that a level IV node is the sentinel of II, III, IV or V in anatomy, and the mechanism remains unclear.

According to the present results, CLNM tends to occur in patients with male gender and LOP/C, while LLNM is more likely to be associated with age <45 years, tumor size >0.5 cm, multifocality, LOP/C and CLNM. PTMC is not an occult cancer and it can act like larger PTC (62). Currently, no effective preoperative examination exists to confirm the existence of LLNM, when clinical examination of cervical lymph node is negative. The present results revealed that 45.5% (30/66) of cases had LLNM and the ratio of II, III, IV and V was 20, 30.3, 25.8 and 4.8%, respectively; therefore, it may not be enough for certain PTMC patients if only CLNM is performed. Therefore, intraoperative frozen section pathological examination of high-risk factors will be useful to direct the surgical approach of PTMC and reduce the regional recurrence. PLLND is recommend intensely if LOP/C and CLNM are performed by intraoperative frozen section pathological examination and must be considered in patients with the age <45 years, tumor size >0.5 cm and multifocal lesions.

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