



ORIGINAL ARTICLE

Predictors for central lymph node metastases in cN0 papillary thyroid microcarcinoma (mPTC): A retrospective analysis of 1304 cases



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Summary *Background:* Presence of lymph node metastases increases the risk of recurrence, but prophylactic central neck node dissection for patients with micropapillary thyroid cancer (mPTC) is controversial. We aim to find the clinical predictors of central lymph node metastases (CLNM) in patients with cN0 mPTC.

Methods: We retrospectively reviewed the clinicopathological and molecular genetic characteristics of 1304 patients with cN0 mPTC operated at the First Hospital of Jilin University between January 1, 2013 and May 31, 2016, all underwent thyroid lobectomy or total thyroidectomy with unilateral or bilateral prophylactic central neck dissection. Univariate and multivariate analysis were used to identify the predictors of CLNM.

Results: 30.7% of cN0 mPTC patients had CLNM. Univariate analysis found CLNM to be associated with younger age (≤ 45), male gender, larger tumor (>0.5 cm), multifocality, bilaterality, capsular invasion, lymphovascular invasion and extrathyroidal infiltration, but not associated with BRAF mutation, tumor location, preoperative TSH and anti-thyroglobulin antibody level. Multivariate logistic regression showed age ≤ 45 years ($p < 0.001$, OR = 2.05), male gender ($p < 0.001$, OR = 1.94), tumor size >0.5 cm ($p < 0.001$, OR = 1.87), bilaterality ($p = 0.003$, OR = 1.86) and capsular invasion ($p = 0.013$, OR = 1.49) to be independent predictors for CLNM in cN0 mPTC patients.

Conclusions: Prophylactic central neck dissection has higher yield for cN0 mPTC patients with age ≤ 45 years, male gender, tumor size >0.5 cm, bilaterality and capsular invasion. BRAF

Abbreviations: CLNM, central lymph node metastasis; ND, neck dissection; CND, central neck dissection; ATG, anti-thyroglobulin antibody.

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mutation is not a predictor for CLNM in cN0 mPTC patients.

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1. Introduction

The incidence of papillary thyroid carcinoma (PTC) which accounts for 80–85% of thyroid cancer has increased worldwide over the past decades.^{1,2} Papillary thyroid microcarcinoma (or micropapillary thyroid cancer, mPTC), defined as a PTC with the maximal diameter of no more than 1.0 cm by World Health Organization,³ account for most of the increased incidence.⁴ Although most patients with PTC have excellent prognosis, some may have metastatic disease. Cervical lymph node metastasis, especially in the central compartment (central lymph node metastasis, CLNM), are found in many patients with PTC, and is associated with an increased risk of local recurrence and mortality.^{1,5} Neck dissection (ND) is recommended for patients with cN1 PTC per American Thyroid Association (ATA) guidelines.⁶ Ultrasound and contrast-enhanced computed tomography are not sensitive in detecting metastatic central neck lymph nodes preoperatively because they are usually small and are obscured by the overlying thyroid gland.⁷ Many CLNM can be found on frozen during the operation in clinical node negative (cN0) patients with mPTC.⁸ It has been reported that 30%–65% of patients with cN0 mPTC had CLNM (detected only on pathology).^{9,10} Some argue that prophylactic central neck dissection (CND) may benefit patients with cN0 mPTC by decreasing local recurrence and improving disease-specific survival.^{11–13} Prophylactic CND may also help more accurately stage the cancer.¹¹ ATA guidelines also allow prophylactic CND in cN0 PTC patients, especially for advanced primary tumors.⁶ Others argue against prophylactic CND because it does not improve survival and it increases the risk of nerve injury and hypoparathyroidism.¹⁴

For the proponents of prophylactic CND knowing which groups of patients have higher rate of nodal metastasis would allow for a more selective use of prophylactic CND in the higher risk group. Some have studied the risk factors for CLNM in patients with PTC,^{15,16} but none have focused on mPTC. In this study, we aim to find the clinicopathologic and molecular genetic factors associated with CLNM in cN0 patients with mPTC.

2. Materials and methods

One thousand three hundred and four consecutive patients with cN0 mPTC who were underwent operations at the First Hospital of Jilin University between January 1, 2013 and May 31, 2016 were included in this retrospective study. Patients with reoperation, history of radiation exposure, familial thyroid cancer and isthmus lesion were excluded. None of the patients had preoperative palpable or suspicious lymph nodes on ultrasound. Micropapillary thyroid

cancer was identified by pathology in all cases. Preoperative fine needle aspiration and intraoperative frozen section are performed routinely to confirm the diagnosis of papillary thyroid cancer. Tumor characteristics such as tumor size, multifocality, capsular invasion and microscopic lymph node metastasis are routinely reported on pathology. The accuracy rate of frozen section diagnosis of mPTC was better than 95%. Patients with bilateral mPTC underwent total thyroidectomy plus bilateral CND (681 cases). Patients with unilateral mPTC underwent lobectomy (590 cases) or total thyroidectomy (33 cases) plus ipsilateral CND. Cohort was divided into two groups according to whether they have central neck node metastasis. Clinicopathological parameters were analyzed. These include age, gender, tumor size, location, multifocality, bilaterality, capsular invasion, extrathyroidal extension, lymphovascular invasion, coexisting Hashimoto thyroiditis, preoperative levels of TSH and anti-thyroglobulin (ATG) antibody. The status of BRAF mutation as a risk factor was also studied, which was detected by ARMS (amplification refractory mutation system)-PCR method. The incidence of hypoparathyroidism and recurrent laryngeal palsy in our study is 6.8% (89 of 1304 cases) and 0.61% (8 of 1304 cases), no permanent complications were observed in all cases.

Statistical analyses were performed with SPSS software (version 17.0; SPSS Inc., Chicago, IL, USA). Chi square or Fisher exact tests and Student's *t* test were used for univariate analysis. Multivariate logistic regression analysis was used to assess the independent risk factors for CLNM. Odds ratios (ORs) with 95% confidence intervals (CIs) were presented for factors that were statistically significant in univariate analysis. Statistical significance was accepted when the *p* value <0.05 (two-sided).

3. Results

3.1. Clinicopathological and molecular genetic characteristics

There were 1117 women and 187 men with mean age of 44.9 ± 9.32 years (range 9–74). Seven hundred and five patients were 45 years old or younger and 599 were older than 45. The average largest tumor diameter was 0.54 ± 0.21 cm; 445 were 0.5 cm or smaller and 859 were larger than 0.5 cm. Tumors were in upper (upper 1/3 part of lobe), middle (mid 1/3 part of lobe) and lower (lower 1/3 part of lobe) region in 335, 283 and 686 patients. Cancers were multifocal in 785 patients and bilateral in 623 patients. Capsular invasion, extrathyroidal extension and lymphovascular invasion were found in 879 (67.4%), 142 (10.9%) and 7 (0.5%) respectively. 435 had Hashimoto thyroiditis. Preoperative serum levels of TSH and ATG

antibody were elevated in 186 (14.3%) and 314 (24.1%) patients. BRAF mutation was analyzed in 456, of which 383 (84.0%) had BRAF V600E mutation. CLNM was found in 400 patients (30.7%) (Table 1).

3.2. Risk factors for CLNM in patients with mPTC

Univariate analysis found CLNM to be associated with younger age (≤ 45), male sex, larger size (>0.5 cm), multifocality, bilaterality, capsular invasion, lymphovascular invasion and extrathyroidal extension. CLNM was not associated with presence of BRAF mutation, location of tumor, coexisting Hashimoto thyroiditis or preoperative TSH and ATG levels (Table 2). Multivariate logistic regression showed

age ≤ 45 years ($p < 0.001$, OR = 2.05), male sex ($p < 0.001$, OR = 1.94), tumor size >0.5 cm ($p < 0.001$, OR = 1.87), bilaterality ($p = 0.003$, OR = 1.86) and capsular invasion ($p = 0.013$, OR = 1.49) to be independent predictors for CLNM in cN0 mPTC patients (Table 3).

4. Discussion

Prophylactic CND for low risk patients with papillary thyroid cancer remains controversial. The decision depends on balancing the incremental risk of node dissection with incremental benefit. One potential strategy is to increase the yield of prophylactic lymph node dissection by operating on selected group. Increasing use of neck ultrasound in China, similar to that in Korea and the United States, has led to an increased in the diagnosis of micropapillary thyroid cancer (mPTC). Most of these patients have no clinically detectable central neck lymph node metastasis (cN0). During the period of our review the consensus and guidelines in China recommended lobectomy and total thyroidectomy as options for mPTC, but prophylactic CND was controversial. Although most patients with mPTC have a favorable prognosis, 2% develop local recurrence¹⁷ and 2.5% have distant metastasis.¹⁵ Presence of lymph node metastasis is one of the most important factors associated with local recurrence and distant metastasis.¹⁸ Studies showed 30–65% of cN0 mPTC have subclinical CLNM.^{9,10} Prophylactic CND may decrease local recurrence, and prevent complications due to repeated operations. It may reduce the use of radioactive iodine¹⁹ by lowering the postoperative level of thyroglobulin.²⁰

Age was one of the most important prognostic factors of PTC. Some studies have shown that cN0 patients ≤ 45 years old to have higher rate of CLNM than older patients,²¹ that ages younger than 45 years was an independent risk factor of CLNM in cN0 patients with mPTC.^{22,23} In contrast, other studies have not found age to be associated with CLNM in mPTC patients.^{24,25} Our study found age ≤ 45 years to be an independent predictor of CLNM in cN0 mPTC (OR = 2.05, 95%CI, 1.583–2.654).

While Jiang et al found no relationship between gender and CLNM in cN0 PTC patients.²⁵ We found male gender to be an independent risk factor for CLNM in cN0 patients with mPTC (OR = 1.935, 95%CI, 1.376–2.722), similar to that found by Chang et al.²⁴

We found that tumor larger than 0.5 cm had a higher risk of CLNM in cN0 mPTC patients (OR = 1.873; 95%CI, 1.381–2.539), similar to what was reported previously.^{10,16}

Because of preferential lymphatic drainage pattern, the location of thyroid cancer may influence where lymph node metastases are found.¹⁶ Cancer in the upper pole of thyroid are associated with higher rate of lateral neck node metastasis, while those in the lower pole have an increased risk of central neck node metastasis.²⁶ Ma et al found that tumor in upper third thyroid had a lower risk of CLNM in cN0 PTC patients.²³ But we found no relationship between tumor location and the rate of central neck node metastasis in cN0 mPTC.

Multifocality and bilaterality have been reported to increase the rate of CLNM in PTC.^{27,28} Multifocal PTC may be a “field defect” with increased development of independent

Table 1 Clinicopathological and molecular genetic characteristics of the 1304 cN0 mPTC patients.

Variables	Number of patients	Percentage (%)
Gender		
Female	1117	85.7
Male	187	14.3
Age		
≤ 45	705	54.1
>45	599	45.9
Tumor size (cm)		
≤ 0.5	445	34.1
>0.5	859	65.9
Location		
Upper	335	25.7
Middle	283	21.7
Lower	686	52.6
Multifocality		
Uni focus	519	39.8
Multi foci	785	61.2
Bilaterality		
Unilateral	623	47.8
Bilateral	681	52.2
Capsular invasion		
No	425	32.6
Yes	879	67.4
Extrathyroidal infiltration		
No	1162	89.1
Yes	142	10.9
Lymphovascular invasion		
No	1297	99.5
Yes	7	0.5
Hashimoto		
No	869	66.6
Yes	435	33.4
BRAF mutation		
No	73	5.6
Yes	383	29.4
Unknown	848	65.0
TSH (preoperative)		
No increased	1118	85.7
Increased	186	14.3
Anti-Tg (preoperative)		
Normal	990	75.9
Increased	314	24.1

Table 2 Comparison of clinical and molecular genetic characteristics for patients of cN0 mPTC with CLNM and those without CLNM.

Variables	LN (-) (n = 904)	LN (+) (n = 400)		p Value
Gender				
Female	800 (88.5)	317 (79.2)	$\chi^2 = 19.272$	$p < 0.01$
Male	104 (11.5)	83 (20.8)		
Age	46.1 ± 9.02	42.2 ± 9.46	t = 7.087	$p < 0.01$
≤45	441 (48.8)	264 (66.0)	$\chi^2 = 33.098$	$p < 0.01$
>45	463 (51.2)	136 (34.0)		
Tumor size (cm)	0.512 ± 0.207	0.608 ± 0.195	t = -7.830	$p = 0.522$
≤0.5	362 (40.0)	83 (20.8)	$\chi^2 = 45.921$	$p < 0.01$
>0.5	542 (60.0)	317 (79.2)		
Location				
Upper	234 (25.9)	101 (25.3)	$\chi^2 = 0.997$	$p = 0.607$
Middle	202 (22.3)	81 (20.2)		
Lower	468 (51.8)	218 (54.5)		
Multifocality				
Uni focus	421 (46.6)	98 (24.5)	$\chi^2 = 56.377$	$p < 0.01$
Multi foci	483 (53.4)	302 (75.5)		
Bilaterality				
Unilateral	541 (59.8)	140 (35.0)	$\chi^2 = 68.605$	$p < 0.01$
Bilateral	363 (40.2)	260 (65.0)		
Capsular invasion				
No	343 (36.4)	82 (20.5)	$\chi^2 = 38.401$	$p < 0.01$
Yes	561 (62.1)	318 (79.5)		
Extrathyroidal infiltration				
No	821 (90.8)	341 (85.3)	$\chi^2 = 8.861$	$p < 0.01 (=0.003)$
Yes	83 (9.2)	59 (14.8)		
Lymphovascular invasion				
No	904 (100)	393 (98.3)	$\chi^2 = 15.905$	$p < 0.01$
Yes	0 (0)	7 (1.8)		
Hashimoto				
No	600 (66.4)	269 (67.3)	$\chi^2 = 0.096$	$p = 0.756$
Yes	304 (33.6)	131 (32.8)		
BRAF mutation				
No	51 (5.6)	22 (5.5)	$\chi^2 = 1.936$	$p = 0.380$
Yes	255 (28.2)	128 (32.0)		
Unknown	598 (66.2)	250 (62.5)		
TSH (preoperative)				
No increased	775 (85.7)	343 (85.8)	t = 0.876	$p = 0.381$
Increased	129 (14.3)	57 (14.2)	$\chi^2 < 0.01$	$p = 0.992$
Anti-Tg (preoperative)				
Normal	684 (75.7)	306 (76.5)	$\chi^2 = 0.106$	$p = 0.745$
Increased	220 (24.3)	94 (23.5)		

Table 3 Multivariate analysis of risk factors of CLNM in cN0 mPTC patients.

Variables	Odds ratio	95%CI	p Value
Age (≤45 years)	2.050	1.583, 2.654	$p < 0.01$
Gender (male)	1.935	1.376, 2.722	$p < 0.01$
Size (>0.5 cm)	1.873	1.381, 2.539	$p < 0.01$
Bilaterality	1.857	1.243, 4.564	$p < 0.01$
Capsular invasion	1.493	1.087, 2.050	$p = 0.013$

cancers or it can be the results of intrathyroidal metastasis via the rich lymphatic system of the thyroid.^{29,30} Multifocality is strongly associated with bilaterality; 84% of mPTC

patients with multifocal tumors also had bilateral tumors.²⁸ We found 86.8% of multifocality to be associated with bilateral tumors. Although we found both multifocality and bilaterality to be associated with the CLNM in cN0 mPTC, only the bilaterality was an independent risk factor of CLNM (OR = 1.875, 95%CI 1.243–4.564).

Capsular invasion is associated with CLNM. The incidence of capsular invasion was higher in patients with CLNM than those without CLNM.^{15,21,31} We found capsular invasion to be an independent risk factor of CLNM in cN0 mPTC patients (OR = 1.493, 95%CI 1.087–2.050), similar to previous study by Gülben.³¹ Lymphovascular invasion and extrathyroidal extension have been found to be associated with an increased risk of CLNM in PTC patients.^{22,32–34}

Although we found both lymphovascular invasion and extrathyroidal infiltration to be associated with CLNM, neither were an independent risk factor of CLNM in cN0 mPTC patients.

Antithyroglobulin antibody, especially with an increase TSH, is an independent predictor of thyroid malignancy^{35,36} and higher preoperative serum TSH level was associated with more advanced PTC.³⁷ Our study, however, did not find any statistical differences of preoperative antithyroglobulin antibody and TSH levels between the two groups ($p = 0.745$, $p = 0.992$, respectively). Coexisting Hashimoto in 33.4% of our patients is not a predictor of CLNM in contrast to other studies.³⁸

BRAF mutation is very common in PTC.³⁹ In our study 84.0% of cN0 mPTC had BRAF mutation. Initial studies showed BRAF mutation to be associated with lymphovascular invasion and metastasis, and higher disease-specific mortality rate in PTC patients,^{38,40} and higher rates of central and lateral lymph node metastasis.⁴¹ This led some researchers to advocate routine CND in patients with BRAF mutation.⁴² Several recent studies, however, found BRAF mutation not to be associated with lymph node metastasis and disease specific survival in PTC patients.^{39,43,44} We also did not find an association between BRAF mutation and CLNM in cN0 mPTC patients.

There are some limitations to this study. It is retrospective and we do not have long term follow up for analysis for recurrence and survival. These cN0 patients with mPTC, however, would be expected have excellent prognosis. Our aim was mainly to determine whether there are factors that may predict the yield of central neck node dissection in this group of patients. So that IF prophylactic lymph node dissection WERE to be performed we would have a higher yield, thus improving the benefit to risk ratio.

In conclusion, we found age ≤ 45 , male gender, tumor size >0.5 cm, bilaterality and capsular invasion to be independent predictors of central neck lymph node metastasis in cN0 mPTC patients. Prophylactic central neck dissection would be expected to have higher yield in patients with these factors. In contrast, BRAF mutation was not a predictor of CLNM in cN0 mPTC patients.

Disclosure statement

The authors have no affiliations with or involvement in any organization or entity with any financial interest in the subject matter or materials discussed in this manuscript.

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