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Risk factors of central lymph node metastasis in cN0 papillary thyroid carcinoma: A study of 529 patients

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

ABCDEF **Keke Liang**
BCDF **Liang He**
BCDEF **Wenwu Dong**
ADEFG **Hao Zhang**

Department of General Surgery, The First Affiliated Hospital of China Medical University, Shenyang, P.R. China

Corresponding Author: Hao Zhang, e-mail: haozhang@mail.cmu.edu.cn

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Background: Lymph node metastasis in papillary thyroid carcinoma (PTC) is common; however, the need for prophylactic central lymph node dissection (CLND) in PTC is still controversial. The objective of this study was to investigate the risk factors of central lymph node metastasis (CLNM) in clinically lymph node-negative (cN0) PTC patients.

Material/Methods: A total of 529 cN0 PTC patients who underwent lobectomy plus isthmusectomy or total thyroidectomy with unilateral or bilateral CLND between 2010 and 2012 were enrolled in this study. Clinicopathologic risk factors for CLNM were studied using univariate and multivariate analysis.

Results: CLNM was found in 238 (45.0%) cases. In univariate analysis, male sex, age <45 years, tumor size >2 cm, tumor located in the middle/lower third of lobe, and multifocality were significantly associated with CLNM ($P<0.05$); extrathyroid extension, Hashimoto's thyroiditis, and TSH value were not associated with CLNM. In multivariate analysis, tumor size >2 cm, age <45 years, multifocality, and tumor located in the middle/lower third of the lobe were independent predictors for CLNM.

Conclusions: Prophylactic CLND should be considered in cN0 PTC patients with the following risk factors: tumor size >2 cm, age <45 years, multifocality, or tumor located in the middle/lower third of the lobe. However, further long-term follow-up studies and multicenter research are needed to better understand these risk factors and the significance of prophylactic CLND.

MeSH Keywords: **CLND • CLNM • Prophylactic • cN0 • Lymph Nodes • Thyroid Neoplasms • Risk Factors**

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Background

Thyroid carcinoma is the most common endocrine malignancy, accounting for approximately 1% of all malignant tumors [1]. Papillary thyroid carcinoma (PTC) is the most common histological subtype, accounting for more than 85% of all cases. Although the prognosis of PTC is good, with 10-year survival rate exceeding 95% and 20-year survival rate exceeding 93%, recurrence is an important factor increasing morbidity and mortality, and cervical lymph node metastasis is the most important variable known to increase the risk of local recurrence [2]. The incidence of cervical lymph node metastasis is high, ranging from 20% to 90%, with an average of 60% [3], and central lymph node metastasis (CLNM) is most common [4,5]. Dissemination of PTC occurs in a stepwise fashion, first to nodes in the tracheoesophageal groove and pre-trachea, and subsequently to nodes in the lateral neck and mediastinum; contralateral cervico-lateral and mediastinal lymph node metastases and skip metastases (negative central and positive lateral or mediastinal lymph nodes) are generally uncommon [6]. Moreover, metastatic papillary thyroid carcinoma with absence of tumor focus in the thyroid gland has also been reported [7]. There is no controversy about therapeutic central lymph node dissection (CLND) in clinically lymph node-positive (cN1) PTC patients. However, the role of prophylactic CLND in the treatment of clinically lymph node-negative (cN0) cases remains controversial [8]. Routine prophylactic central lymph node dissection may be overtreatment in many cN0 patients. Therefore, identification of risk factors associated with CLNM may help tailor appropriate surgical strategies for cN0 PTC patients. The aim of our study was to determine the risk factors of CLNM and to identify a subset of cN0 PTC patients who may benefit from CLND in initial surgery.

Material and Methods

Patients

This study was approved by the Ethics Committee of the First Affiliated Hospital of China Medical University. A total of 529 cN0 PTC patients who were initially treated in the First Affiliated Hospital of China Medical University between January 2010 and November 2012 were enrolled. They consisted of 118 (22.3%) males and 411 (77.7%) females, and the age ranged from 13 to 74 years (median, 45 years). Patients who underwent therapeutic neck dissection for clinically positive lymph nodes in the central or lateral compartment were excluded. The diagnosis of PTC and nodal metastasis was confirmed by pathological specimens. We performed unilateral thyroid lobectomy plus isthmusectomy with ipsilateral CLND for unilateral PTC patients and total thyroidectomy with bilateral CLND for bilateral PTC patients.

Clinicopathological variables assessed

The following variables were used to analyze risk factors of CLNM: sex, age at initial treatment, tumor size, tumor location in thyroid lobe, extrathyroid extension, multifocality, TSH value, and Hashimoto's thyroiditis (HT). Tumor size, multifocality, and HT were all confirmed by pathological findings. Extrathyroid extension was defined as a tumor extending beyond the thyroid capsule to invade subcutaneous soft tissues, larynx, trachea, esophagus, or recurrent laryngeal nerve based on intraoperative findings, and multifocality was defined as more than 1 tumor lesion in the thyroid. Tumor size in multifocal cases was measured according to maximum diameter of the primary tumor. TSH value was evaluated within 1 month before surgery. T stage was decided according to the 2010 AJCC staging system [9].

Statistical analysis

Statistical analysis was performed using SPSS 18.0 software. Data are presented as the mean \pm SD. Univariate analysis by the χ^2 test was performed to investigate the relationships between CLNM and clinicopathological variables. Multivariate analysis was performed by binary logistic regression. Statistical significance was assumed when $P < 0.05$.

Results

Clinicopathological characteristics

The mean size of primary tumors was 1.6 ± 1.1 cm, (range, 0.2–7.0 cm). Multifocal lesions were found in 79 (14.9) patients. For solitary lesion, 113 (21.4%) lesions were in the upper third of lobe, 173 (32.7%) were in the middle third, and 164 (31.0%) were in the lower third. Extrathyroidal extension was found in 6 (1.1%) patients. The number of patients in T1/T2/T3/T4 stages were 364 (68.8%), 73 (13.8%), 86 (16.3%), and 6 (1.1%), respectively. HT was detected in 116 (21.9%) patients, and the mean value of TSH was 1.99 ± 1.66 (range, 0.02–14.25 mIU/L). Central lymph node metastases were found in 238 (45.0%) patients. The mean numbers of total and positive lymph nodes collected during CLND were 3.6 ± 3.2 (range, 0–16) and 1.4 ± 1.9 (range, 0–11), respectively (Table 1).

Risk factors for CLNM

Univariate analysis showed that CLNM was significantly associated with male sex, age < 45 years, tumor size > 2 cm, tumor located in the middle/lower third of the lobe, and multifocality ($P < 0.05$). However, extrathyroidal extension, Hashimoto's thyroiditis, and TSH value were not significantly associated with CLNM ($P > 0.05$) (Table 2).

Table 1. Characteristics of patients.

Characteristics	Values
No. of patients	529
Gender (M/F) (%)	118/411 (22.3/77.7)
Age (yrs), mean ±SD (range)	44.5±11.1 (13–74)
Tumor size (cm), mean ±SD (range)	1.6±1.1 (0.2–7.0)
Location of the primary tumors	
Solitary lesion, n (%)	450 (85.1)
upper/middle/lower third, n(%)	113/173/164 (21.4/32.7/31.0)
Multifocal lesions, n (%)	79 (14.9)
in a unilateral lobe/in both lobes, n(%)	13/66 (2.5/12.4)
Extrathyroid extension, n (%)	6(1.1)
T1/T2/T3/T4, n (%)	364/73/86/6 (68.8/13.8/16.3/1.1)
TSH (mIU/L), mean ±SD (range)	1.99±1.66 (0.02–14.25)
Hashimoto's thyroiditis, n (%)	116 (21.9)
Central lymph node metastasis, n (%)	238(45.0)
Dissected lymph node, mean ±SD (range)	3.6±3.2 (0–16)
Metastatic lymph node, mean ±SD (range)	1.4±1.9 (0–11)

In multivariate analysis, tumor size >2 cm, age <45 years, multifocality, and tumor located in the middle/lower third of the lobe were independent predictors for CLNM ($P<0.05$) (Table 3).

Discussion

Despite good overall prognosis of PTC, recurrence of the disease after initial surgical cure remains problematic [10]. CLNM is the most important variable known to increase the risk of local recurrence [2]. In our study, CLNM was detected in 45.0% of cNO patients, which was similar to results of previous studies (42.9% [6], 44.1% [2] and 46.1% [11]).

The indication of prophylactic central lymph node dissection is always a major issue in the management of cNO PTC patients, which mainly focuses on the balance of the potential benefits and postoperative complications. CLND has the advantage of removing potential sources of recurrence, reducing

Table 2. Clinicopathologic variables and central lymph node metastasis.

Variables	CLNM number (%)	P value
Gender		0.012
Male	65 of 118 (55.1)	
Femal	173 of 411 (42.1)	
Age (yrs)		<0.001
<45	141 of 256 (55.1)	
≥45	97 of 273 (35.5%)	
Tumor size (cm)		<0.001
≤1	86 of 239 (36.0)	<0.001 ^a
1<Φ≤2	78 of 171 (45.6)	
2<Φ≤4	67 of 105 (63.8)	
>4	7 of 14 (50.0)	
Location of solitary tumor		0.033
Upper third of lobe	37 of 113 (32.7)	0.047 ^b , 0.011 ^c , 0.500 ^d
Middle third of lobe	77 of 173 (44.5)	
Lower third of lobe	79 of 164 (48.2)	
Multifocality		0.020
Solitary	193 of 450 (42.9)	
Multifocal	45 of 79 (57.0)	
Extrathyroid extension		0.509
Absent	234 of 523 (44.7)	
Present	4 of 6 (66.7)	
TSH (mIU/L)		0.752
<2.5	176 of 398 (44.2)	
≥2.5	60 of 131 (45.8)	
Hashimoto 's thyroiditis		0.802
Absent	187 of 413 (45.3)	
Present	51 of 116 (44.0)	

^a (tumor size >2 vs. tumor size ≤2 cm), ^b (upper third vs. middle third), ^c (upper third vs. lower third), ^d (middle third vs. lower third).

the morbidity of a re-operation, accurately staging these tumors, and optimizing postoperative treatment and follow-up, but postoperative complications such as hypocalcemia and recurrent laryngeal nerve injury may increase with greater use

Table 3. Multivariate analysis for risk factors of central lymph node metastasis.

Variables	β (SE)	P value	Exp (β)	95% CI of exp (β)
Gender (male vs. female)	0.394 (0.226)	0.082	1.483	0.951~2.311
Age (<45 vs. \geq 45 yrs)	0.824 (0.188)	0.000	2.280	1.577~3.298
Size (>2 vs. \leq 2cm)	0.938 (0.224)	0.000	2.555	1.646~3.967
Location(middle/lower vs. upper third)	0.433 (0.220)	0.049	1.542	1.003~2.372
Multifocality(positive vs. negative)	0.731 (0.261)	0.005	2.077	1.244~3.468
Extrathyroidal extension (positive vs. negative)	0.942 (0.947)	0.320	2.565	0.401~16.428
TSH (\geq 2.5 vs. <2.5mIU/L)	0.150 (0.231)	0.517	1.161	0.739~1.825
Hashimoto's thyroiditis (present vs. absent)	0.041 (0.229)	0.857	1.042	0.665~1.632
Constant	-1.399 (0.238)	0.000	0.247	

of prophylactic CLND [12–14]. Therefore, it is reasonable to perform selective CLND if the presence of CLNM can be predicted preoperatively.

The sensitivity of preoperative ultrasound (US) in detecting pathological cervical lymph nodes is 62%, with lower sensitivity for central lymph nodes than for lateral lymph nodes (55% vs. 65%) [15]. Kouvaraki et al. had the similar result, with a sensitivity of 53.3% [16]. Thus, it is not a reliable indicator of node negativity and the treatment decision cannot be based solely on it.

Recently, several studies have described clinicopathological factors associated with CLNM in patients with PTC, but results from those studies were not consistent [2,5,10–16]. In our study, tumor size >2 cm, age <45 years, multifocality, and tumor located in the middle/lower third of the lobe were independent predictors for CLNM.

As shown in Table 3, tumor size >2 cm was the strongest predictor of CLNM on multivariate analysis in our study. Several studies have shown that tumor size was significantly associated with CLNM, but the cutoff points were different. Ito [17] reported tumor size >2 cm was the strongest predictor of CLNM in PTC, Bozec [18], Choi [19] and Koo [8] reported tumor size >1 cm was associated with CLNM in PTC, while Zhang [20] and Kim [10] reported tumor size >6 mm and tumor size >5 mm, respectively, were associated with CLNM in PTMC. In our study, the rate of CLNM was highest in the group with tumor size >2 cm and tumor size \leq 4 cm, and tumor size >2 cm was significantly associated with CLNM.

Patients under 45 years of age exhibit a better prognosis than older patients, because all patients under 45 years without distant metastasis are classified in the stage I group irrespective of T stage and N status according to the 2010 AJCC staging system [9]. However, in our study there was statistically

significant association between age <45 years and CLNM, which is similar to previous studies [18,20].

In agreement with Wang [21] and Zhang [20], we found that a tumor located in the middle/lower third of the lobe was significantly associated with CLNM, while there was no significant difference for CLNM between the middle and lower third of the lobe. This may be associated with the lymphatic drainage of the thyroid gland. TSH and HT were not risk factors, which was also consistent with the previous study [22]. Multifocality was an independent predictor of CLNM in our study, which is agreement with the previous report [2].

In many reports, extrathyroidal extension was a risk factor for CLNM [6,10,21], but it was not in our study. This may be because the number of patients with extrathyroid extension was small, or because only significant extension was diagnosed in our study.

Our study has some limitations that must be considered. First, this study was a retrospective analysis, and prognosis was not investigated. Second, our study population was from a single center. Thus, multicenter research and long-term follow-up are needed to better understand the risk factors and the significance of prophylactic CLND.

Conclusions

In our study, CLNM were found in nearly half of all cN0 PTC patients when prophylactic CLND was performed. Our study also showed that tumor size >2 cm, age <45 years, multifocality, and a tumor located in the middle/lower third of the lobe were independent predictors for CLNM. However, these data should be interpreted with caution because our study was a retrospective analysis and lacked data regarding prognostic significance. Thus, further long-term follow-up studies and

multicenter research are needed to better understand these risk factors and the significance of prophylactic CLND.

Conflict of interests

The authors declare no conflicts of interests.

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