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

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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 pretrachea, 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 (cN+) 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 to 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 ±SD. Univariate analysis by the χ² 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 (21.9%) 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 in thyroid lobe, extrathyroid extension, multifocality, TSH value, HT were all confirmed by pathological findings. Extrathyroidal extension, Hashimoto’s thyroiditis, and TSH value were not significantly associated with CLNM (P>0.05) (Table 2).

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).
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 cN0 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 cN0 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 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.
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 ≤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

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

| Variables                                | β (SE)     | P value | Exp (β) | 95% Cl of exp (β) |
|------------------------------------------|-----------|---------|---------|-------------------|
| Gender (male vs. female)                 | 0.394 (0.226) | 0.082   | 1.483   | 0.951–2.311       |
| Age (<45 vs. ≥45 yrs)                    | 0.824 (0.188) | 0.000   | 2.280   | 1.577–3.298       |
| Size (≥2 vs. <2 cm)                      | 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 (≥2.5 vs. <2.5 mIU/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   |                    |
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.

References:

1. Lundgren CI, Hall P, Dickman PW, Zedenius J: Clinically significant prognostic factors for differentiated thyroid carcinoma: a population-based, nested case-control study. Cancer, 2006; 106: 524–31
2. Wang Q, Chu B, Zhu J et al: Clinical analysis of prophylactic central neck dissection for papillary thyroid carcinoma. Clin Transl Oncol, 2013; 1–5
3. Rotstein L: The role of lymphadenectomy in the management of papillary carcinoma of the thyroid. J Surg Oncol, 2009; 99: 186–88
4. Robbins KT, Shaha AR, Medina JE et al: Consensus statement on the classification and terminology of neck dissection. Arch Otolaryngol Head Neck Surg, 2008; 134: 534–38
5. Roh JL, Kim JM, Park CI: Central compartment reoperation for recurrent/persistent differentiated thyroid cancer: patterns of recurrence, morbidity, and prediction of postoperative hypocalcemia. Ann Surg Oncol, 2011; 18: 1312–18
6. Roh JL, Kim JM, Park CI: Central lymph node metastasis of unilateral papillary thyroid carcinoma: patterns and factors predictive of nodal metastasis, morbidity, and recurrence. Ann Surg Oncol, 2011; 18: 2245–50
7. Anil S, Radu B, Ricardo L: Metastatic papillary thyroid carcinoma with absence of tumor focus in thyroid gland. Am J Case Rep, 2013; 14: 73–75
8. Koo BS, Choi EC, Yoon YH et al: Predictive factors for ipsilateral or contralateral central lymph node metastasis in unilateral papillary thyroid carcinoma. Ann Surg, 2009; 249: 840–44
9. NCCN Clinical Practice Guidelines in Oncology. Thyroid carcinoma, Version 2, 2012
10. Kim BY, Jung CH, Kim IJ et al: Impact of clinicopathologic factors on subclinical central lymph node metastasis in papillary thyroid microcarcinoma. Yonsei Med J, 2012; 53: 924–30
11. Muller M, Schulte KM: Central cervical lymph node metastases in papillary thyroid cancer: a systematic review of imaging-guided and prophylactic removal of the central compartment. Clin Endocrinol (Oxf), 2012; 76: 131–36
12. Costa S, Giugliano G, Santoro L et al: Role of prophylactic central neck dissection in cN0 papillary thyroid cancer. Acta Otorhinolaryngologica Ital, 2009; 29: 61–69
13. Carling T, Long WD, Udelsman R: Controversy surrounding the role for routine central lymph node dissection for differentiated thyroid cancer. Curr Opin Oncol, 2012; 22: 30–34
14. Ito Y, Tomoda C, Uruno T et al: Clinical significance of metastasis to the central compartment from papillary microcarcinoma of the thyroid. World J Surg, 2006; 30: 91–99
15. Ahn JH, Lee JH, Yi JS et al: Diagnostic accuracy of CT and ultrasonography for evaluating metastatic cervical lymph nodes in patients with thyroid cancer. World J Surg, 2008; 32: 1552–58
16. Kouvaraki MA, Shapiro SE, Fornage BD et al: Role of preoperative ultrasonography in the surgical management of patients with thyroid cancer. Surgery, 2003; 134: 946–54
17. Ito Y, Fukushima M, Higashiyama T et al: Tumor size is the strongest predictor of microscopic lymph node metastasis and lymph node recurrence of N0 papillary thyroid carcinoma. Endocr J, 2013; 60: 113–17
18. Bozec A, Dassonville Q, Chamorey E et al: Clinical impact of cervical lymph node involvement and central neck dissection in patients with papillary thyroid carcinoma: a retrospective analysis of 368 cases. Eur Arch Otorhinolaryngol, 2011; 268: 1205–12
19. Choi YJ, Yun JS, Kook SH et al: Clinical and Imaging Assessment of Cervical Lymph Node Metastasis in Papillary Thyroid Carcinomas. World J Surg, 2012; 34: 1494–99
20. Zhang L, Wei W, 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: 1250–57
21. Wang W, Gu J, Shang J, Wang K: Correlation analysis on central lymph node metastasis in 276 patients with cN0 papillary thyroid carcinoma. Int J Clin Exp Pathol, 2013; 6: 510–15
22. Kim SS, Lee BJ, Lee JC et al: Coexistence of Hashimoto’s thyroiditis with papillary thyroid carcinoma: The influence of lymph node metastasis. Head Neck, 2011; 33: 1272–77

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