

Original Article

The incidence and predictive factors for central lymph node metastasis in unilateral papillary thyroid carcinoma

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Abstract: Purpose: Although occult central lymph node (LN) metastases in papillary thyroid carcinoma (PTC) are common, the efficacy of prophylactic central lymph node dissection (CLND) remains controversial. This study aimed to investigate the incidence and the risk factors for occult ipsilateral central LN metastasis in patients with unilateral PTC and a clinically negative neck (cNO). Methods: We reviewed a retrospective protocol of 1036 unilateral PTC patients with clinically node-negative necks who have received thyroidectomy and ipsilateral CLND from January 2014 to January 2015. The relationships between metastatic LNs in the ipsilateral central compartment and clinico-pathologic factors such as age, gender, size of primary tumor, number of tumor foci and capsular invasion were analyzed. Results: Occult ipsilateral central LN metastasis was present in 25.3% (262/1036) of these patients with unilateral PTC. Multivariate analysis showed that age <45 years, male gender, tumor size >1 cm, multiplicity and capsular invasion were independent risk factors for the presence of ipsilateral central LN metastasis ($P < 0.05$). Conclusions: Ipsilateral CLND, performed during the initial thyroid surgery, may be effective in the management of male patients (<45 years) with unilateral PTC with tumor size >1 cm, multiplicity and capsular invasion.

Keywords: Central, lymph node, metastasis, papillary thyroid carcinoma, unilateral

Introduction

Papillary thyroid carcinoma (PTC), the most common endocrine malignancy [1], accounts for about 80% of thyroid cancers and is the sixth most common cancer with the most rapid increase in women [2]. With the wide use of ultrasound (US) and US-guided fine-needle aspiration (FNA), more cases of PTC are detected [3]. Cervical lymph node (LN) metastasis is common in PTC patients, ranging from 30 to 80% [4-6]. Dissemination of PTC occurs in a stepwise pattern, first to nodes in the trachea-esophageal groove and pre-trachea, and subsequently to nodes in the lateral neck and mediastinum. Contralateral cervico-lateral and mediastinal lymphnode metastases and skip metastases (negative central and positive lateral or mediastinal lymph nodes) are generally uncommon [7]. Therefore, the central compartment is the common region of lymph nodes metastases from PTC, especially in patients

with clinically node-negative (cNO). Metastasis in the central LNs is an independent risk factor of loco-regional recurrence and can adversely affect survival [8, 9]. Thus, according to the guidelines of revised American Thyroid Association (ATA), prophylactic central lymph node dissection (CLND) has been recommended for patients with high-risk thyroid cancer [10]. However, with the increased extent of surgery of CLND, it may increase the postoperative complications, including recurrent nerve paralysis and hypoparathyroidism [11]. So the need for prophylactic CLND is one of the ongoing controversies in the management of patients with cNO PTC even though cervical LN metastases are quite common.

The aim of this study was to investigate the incidence and the predictive factors for the presence of occult ipsilateral central lymph node metastasis, and evaluate the role of prophylactic CLND in cNO patients with unilateral PTC.

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Table 1. Basic characteristics of 1036 patients with cNO PTC

Characteristics	Values
Gender (M/F)	206/830
Age (years), median (range)	46.0 (12-78)
Tumor size (cm), mean \pm SD (range)	0.77 \pm 0.57 (0.1-4.5)
Multifocal primary lesions, n (%)	192 (18.5)
Capsular invasion, n (%)	486 (46.9)
Central lymph node metastasis, n (%)	262 (25.3)
Dissected lymph node, mean \pm SD (range)	3.22 \pm 2.82 (0-18)
Metastatic lymph node, mean \pm SD (range)	0.54 \pm 1.27 (0-16)

M indicates male; F, female; SD, standard deviation.

Table 2. Univariate analysis of clinic-pathologic factors related to central LN metastases in 1036 patients with unilateral PTC

Variables	No. Patients With central LN metastasis (%)	P*
Age, years		0.000
<45	154/466 (33.0)	
\geq 45	108/570 (18.9)	
Gender		0.000
Male	74/206 (35.9)	
Female	188/830 (22.7)	
Tumor size		0.000
\leq 1 cm	187/855 (21.9)	
>1 cm	75/181 (41.4)	
Focality		0.013
Solitary	200/844 (23.7)	
Multiple	62/192 (32.3)	
Capsular invasion		0.000
Yes	159/486 (32.7)	
No	103/550 (18.7)	

* $P < 0.05$ by the χ^2 test or Fisher exact test.

Materials and methods

Study populations

Patients with unilateral PTC undergoing thyroidectomy and ipsilateral CLND at the Department of Head and Neck Surgery of Zhejiang Cancer Hospital between January 2014 and January 2015 were enrolled for this retrospective study. Patients with clinically node-negative necks, who were diagnosed with unilateral PTC by fine needle aspiration preoperatively or frozen section intraoperatively and treated with thyroidectomy and ipsilateral CLND, were included in this study. The management of contralateral thyroid

gland included preservation, partial, subtotal or total resection. Patients who had non-papillary thyroid carcinomas and those who underwent therapeutic neck dissection for clinically positive LNs in the central or lateral compartment of the neck were excluded. Patients who had undergone surgery for benign thyroid disease, previous radiation therapy of the neck, were also excluded from the study. Consequently, a total of 1036 consecutive unilateral PTC patients with clinically node-negative necks who underwent thyroidectomy with ipsilateral

CLND were enrolled in this study. The study was approved by the Institutional Review Board of Zhejiang Cancer Hospital.

Central lymph node dissection

According to the American Thyroid Association classification [10, 12], boundaries of the CLND were as follow: superiorly to the cricoid cartilage, inferiorly to the innominate vein, laterally to the carotid sheaths, and dorsally to the prevertebral fascia. Lymph nodes in this compartment included the pretracheal and paratracheal nodes, prelaryngeal (Delphian) node, and perithyroidal nodes including the lymph nodes along the recurrent laryngeal nerves [13]. All patients were performed with prophylactic ipsilateral CLND.

Statistical analysis

All statistical analyses were performed by the SPSS version 18.0 software. Univariate analysis by the Pearson χ^2 test or Fisher exact test was performed to investigate the relationships between central LN metastases and patient demographics (age and gender) or primary tumor pathology. Multivariate analysis was performed by binary logistic regression for variables with $P < 0.05$ on univariate analysis.

Results

Clinicopathological characteristics

Table 1 showed the characteristics of 1036 patients. There were 206 males and 830 females, ranging in age from 12 to 78 years (median age: 46.0 years). The mean size of the primary tumor was 0.77 \pm 0.57 cm (range, 0.1-

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Table 3. Multivariate logistic regression for ipsilateral central lymph node metastasis

Variables	B (SE)	P	Exp (β)	95% CI of exp (β)
Age <45 years	-0.709 (0.151)	0.000	0.492	0.366-0.661
Male gender	-0.618 (0.175)	0.000	0.539	0.383-0.759
Tumor size >1 cm	0.807 (0.187)	0.000	2.242	1.554-3.234
Multiple tumor	0.458 (0.184)	0.013	1.581	1.103-2.266
Capsular invasion	0.572 (0.157)	0.000	1.771	1.302-2.410
Constant	-1.370 (0.283)			

SE indicates standard error; Exp (β), odds ratio; CI, confidence interval.

4.5 cm), and 82.5% (855/1036) of patients had tumors ≤ 1 cm. The mean number of removed and metastatic LNs in CLND was 3.22 ± 2.82 (range, 0-18) and 0.54 ± 1.27 (range, 0-16), respectively. Multifocal primary lesions were observed in 192 (18.5%) patients. Capsular invasion of the primary tumor was found in 486 (46.9%) patients. The rate of occult metastasis of LNs in central compartment was 25.3% (262/1036).

Risk factors for central lymph node metastasis (CLNM)

The relationships between ipsilateral CLNM and clinic-pathologic factors in the 1036 unilateral PTC patients were analyzed. Univariate analysis (**Table 2**) showed that ipsilateral CLNM was significantly associated with male patients, age <45 years, primary tumor size >1 cm, multifocal primary lesions and the presence of capsular invasion ($P < 0.05$). In the multivariate analysis (**Table 3**), the rate of ipsilateral CLNM was significantly higher in male patients ($P < 0.05$, odds ratio = 0.539), age <45 years ($P < 0.05$, odds ratio = 0.492), and in cases of tumor with a maximal diameter of greater than 1 cm ($P < 0.05$, odds ratio = 2.242), multifocal primary lesions ($P < 0.05$, odds ratio = 1.581), and the presence of capsular invasion ($P < 0.05$, odds ratio = 1.771).

Discussion

Despite excellent prognosis of PTC, recurrence of the disease after initial surgery remains problematic [14]. Several studies have reported a recurrence risk rate ranging from 0% to 9% for clinically node-negative PTC patients [10]. CLNM is the most important risk factor for local recurrence [15]. However, the indication of prophylactic central lymph node dissection is

always the subject of lively debate in literature in the management of cNO PTC patients. The benefits of prophylactic CLND in cNO PTC patients appear to be correlated with incidences of postoperative complications. CLND may diminish local recurrence and improve disease specific survival from clearing metastatic disease and decrease the postoperative stimulated serum thyroglobulin level significantly than without CLND

[16-19]. However, postoperative hypoparathyroidism was often cited in arguments against prophylactic CLND in the treatment of PTC [20, 21], and the incidence of transient hypoparathyroidism after CLND ranged between 14% and 44% [22]. Moreover, the rate of permanent hypoparathyroidism after total thyroidectomy with prophylactic CLND was between 0% and 14.3% [23]. Therefore, the balance between benefit and complication of prophylactic CLND plays an important role for the CNO PTC patients. But as the presence of multifocal thyroid nodules and surrounding structures in the central neck, high-resolution US could not sufficiently assess central compartment nodes [24, 25]. So it is important to evaluate the high-risk patients for central LN metastasis and determine the prophylactic ipsilateral CLND for unilateral PTC patients with clinically node-negative.

In the literature, several studies have described clinic-pathological factors associated with CLNM in patients with PTC, but results from those studies were not consistent. A majority of studies indicated that a primary tumor size >1 cm was a risk factor of CLNM [26-29] and supported the routine central lymph-node dissection for PTC >1 cm in diameter [30]. However, a retrospective study of 83 subjects revealed no statistically significant difference regarding the risk of CLNM between patients with micro-carcinomas and patients with tumor larger than 1 cm, even with an 18.8% incidence of metastatic disease in tumor size <5 mm [31]. In our experience, the univariate statistical test correlated significantly the tumor size >1 cm to the likelihood of developing CLNM. The data in literature regarding age and gender are conflicting. Females were more susceptible to papillary thyroid carcinoma with significant correlation

between incidence of PTC and estrogen level [32]. Some studies stated that risk of recurrence disease in men was greater than women [33, 34]. Males were more vulnerable to developing positive lymph node involvement than females in our study. Some authors considered age <45 years as a risk factor of CLNM [35, 36], others hold that the risk increases in patients with age \geq 45 years [6, 34, 37]. We also found that multifocality of primary tumor and capsule invasion were associated with the higher rate of central LN metastasis, in agreement with previous results in the literature [1, 38, 39]. In conclusion, our study revealed that the risk of ipsilateral central LN metastasis was significantly increased in male patients, age <45 years, tumor size >1 cm, multifocality of primary tumor and the presence of capsular invasion. In multivariate analysis, above-mentioned variables were the independent risk factors for the presence of ipsilateral central LN metastasis. We strongly advised prophylactic ipsilateral CLND for the PTC patients with these high risk clinic-pathological characteristics.

Some limitations in this study were as follow: (1) the lack of data on the postoperative complications; (2) the variety of surgical extent of thyroidectomy (lobectomy, sub-to total thyroidectomy); (3) the lack of data on the recurrence and survival rate after prophylactic ipsilateral CLND; (4) the short duration of follow-up. We plan to examine the surgical complications, recurrence, and survival rates through long-term follow-up after operation.

A large proportion of patients with unilateral PTC have subclinical metastases in the central neck compartment. Male patients, with age <45 years, tumor size >1 cm, multifocality and capsular invasion are at a high risk of metastasis to the ipsilateral central neck. As occult central metastasis is difficult to diagnose preoperatively, gender, age, the size of primary tumors, the presence of multifocality and capsular invasion determined by intraoperative frozen-section appear to be variable to guide the necessity of prophylactic ipsilateral CLND in unilateral PTC patients with clinical node-negative.

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Disclosure of conflict of interest

None.

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