RESEARCH ARTICLE

Risk Factors for Nodal Metastasis in cN0 Papillary Thyroid Microcarcinoma

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Abstract

Background: Despite the majority of papillary thyroid microcarcinoma (PTMC) patients having an excellent prognosis, cervical lymph node metastases are common. The purpose of this study was to investigate the incidence and the predictive risk factors for occult central compartment lymph node metastasis (CLNM) in PTMC patients. Materials and Methods: 178 patients with clinically node-negative (cN0) PTMC undergoing prophylactic central compartment neck dissection in our hospital from January 2008 to Jun 2010 were enrolled. The relationship between CLNM and the clinical and pathological factors such as gender, age, tumor size, tumor number, tumor location, extracapsular spread (ECS), and coexistance of chronic lymphocytic thyroiditis was analyzed. Results: Occult CLNM was observed in 41% (73/178) of PTMC patients. Multivariate analysis showed that male gender, tumor size (≥6mm) and ECS were independent variables predictive of CLNM in PTMC patients. Conclusions: Male gender, tumor size (≥6mm) and ECS were risk factors of CLNM. We recommend a prophylactic central lymph node dissection (CLND) should be considered in PTMC patients with such risk factors.

Keywords: Papillary thyroid microcarcinoma - central lymph node dissection - central lymph node metastasis

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Introduction

Papillary thyroid microcarcinoma (PTMC) is defined as a papillary thyroid carcinoma(PTC) with a lesion measuring 1 cm or less in maximal diameter according to the 2004 World Health Organization classification of thyroid tumors (DeLellis et al., 2004). It has been generally accepted that the majority of PTMC patients has an excellent prognosis. However, this view has been challenged with new researches reporting increased local recurrence rates (White et al., 2007) and reduced survival with regional LNM (Hughes et al., 2010). For PTMC, cervical lymph node metastases are common, with an incidence between 30% and 60% (Hay et al., 2008; He et al., 2012). Most surgeons agree with therapeutic cervical lymph node dissection in clinically node-positive PTC patients, however, prophylactic central neck lymphadectomy in the treatment of cN0 PTMC is controversial (Mazzaferri et al., 2009). The purpose of this study is to determine the predictive risk factors for LNM at presentation in PTMC. The outcome of the study could assist in making a more appropriate selection of patients for prophylactic neck dissection.

Materials and Methods

This retrospective cohort study was performed of a single institutional database of patients with histologically proven papillary thyroid carcinoma at Peking Union Medical College Hospital from January 2008 to Jun 2010. All patients underwent pre-operative examination by US to evaluate the size of tumor and the presence of LNM. All patients were diagnosed with PTMC pre-operatively by fine-needle aspiration biopsy or intra-operatively on frozen section. Patients with bilateral PTC underwent total thyroidectomy (TT) and bilateral prophylactic central lymph node dissection (CLND), while patients with unilateral PTC underwent TT or unilateral lobectomy plus isthmusectomy and ipsilateral CLND. Patients with PTC of >1cm, evident preoperative abnormal lymph nodes, distant metastasis or previous operation for PTC were excluded. Of the 919 patients treated surgically for PTC from January 2008 to Jun 2010, 178 patients satisfied inclusion criteria.

Patients were divided into two groups according to central compartment lymph node status. The relationship between CLNM and the clinical and pathological factors such as gender, age, tumor size, tumor number, tumor location, extracapsular spread(ECS), and coexistance of chronic lymphocytic thyroiditis was analyzed.

Statistical analysis was performed using SPSS17.0 software. Data were compared for statistical analysis using the chi-square tests or Fisher`s exact test to evaluate differences between qualitative variables, and using the Students t test to compare quantitative variables, multivariate logistic regression analysis was performed to identify the multivariate correlates of central compartment LNM, $p<0.05$ was considered significant.

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Results

178 patients were included in this study among whom 141 were female and 37 were male with a mean age of 46 years. Patients characteristics were shown in Table 1. Median tumor size was 7mm, with 95 tumors (53.4%)<6mm and 83 tumors (46.6%) ≥6mm in diameter. Multifocal PTMC was present in58 cases (32.6%) and extracapsular spread (ECS) was found in 20 cases (11.2%), 42 cases (23.6%) had chronic lymphocytic thyroiditis. The number of patients found to have involved central neck lymph nodes on final pathology was 73 of 178 (41%). The clinical and pathological characteristics of patients are summarized between LNM positive group and LNM negative group in Table 2. Male gender, tumor size (≥6mm), multifocality and ECS were significantly related to central compartment of LNM (p<0.05). There were no significant differences in the age and other tumor pathologic characteristics. A multivariate analysis was performed to determine whether these parameters were independently correlated with central comparment LNM. Male gender, tumor size (≥6mm) and ECS turned out to be independently predictive factors for central compartment LNM (Table 3).

Table 1. Characteristics of Patients with Papillary Thyroid Microcarcinoma

		Total(%)
Gender	Male	37 (20.8)
	Female	141 (79.2)
Age	<45	99 (55.6)
	≥45	79 (44.4)
Tumor size	<6mm	95 (53.4)
	≥6mm	83 (46.6)
Multifocality	Unifocal	120 (67.4)
	Multifocal	58 (32.6)
Tumor bilaterality	unilateral	123 (69.1)
	bilateral	55 (30.9)
ECS	Present	20 (11.2)
	Absent	158 (88.8)
Chronic lymphocytic thyroiditis		
	Present	42 (23.6)
	Absent	136 (76.4)
Central compartment LNM		
	Present	73 (41.0)
	Absent	105 (59.0)
	Median nodes removed	6
	Median positive nodes	1

Table 2. Relationship of Clinical and Histopathologic Factors for Central CLNM

	Nodal status in Central Compartment		P value
	N+(n=73)	N-(n=105)	
Gender			0.01
Male	22	15	
Female	51	90	
Age			0.297
<45	44	55	
≥45	29	50	
Tumor size			0.002
<6mm	29	66	
≥6mm	44	39	
Multifocality			0.002
Unifocal	40	80	
Multifocal	33	25	
Tumor bilaterality			0.143
unilateral	46	77	
bilateral	27	28	
ECS			0.005
Present	14	6	
Absent	59	99	
Chronic lymphocytic thyroiditis			0.099
Present	13	29	
Absent	60	76	

Table 3. Multivariate Logistic Regression for Central Compartment LNM of PTMC

Variables	B	p value	OR	95% CI of Exp
Sex	-2.011	0.001	0.134	0.045-0.395
Size	1.888	0.002	6.606	2.043-21.363
Number	0.644	0.189	1.904	0.728-4.982
ECS	-1.673	0.008	0.188	0.055-0.641
Constant	2.612	0.025	13.62	

*CI=confidence interval; OR=odds ratio; PTMC=papillary thyroid microcarcinoma; SE=standard error

Discussion

The incidence of PTMC has been increasing within recent 5 years with the extensive use of thyroid ultrasonography in routine physical examination (Palazzo FF et al., 2006). Although it has been accepted that patients with PTMC have a good prognosis (C.I. Lundgren, et al., 2006), cervical lymph node metastases are common, with an incidence between 30% and 60%. However, the sensitivity for detecting central LNM in PTC patients using sonography is poor. Choi et al reported that the sensitivity of ultrasound for detecting central LNM is only 40% even when the nodes are≥5mm (Choi et al., 2010). Unfortunatly, most of central lymph node metastases are <5mm (Vergez et al., 2010). We observed approximately 40% of patients who underwent central neck dissection had lymph node involvement despite of negative preoperative physical examination and ultrasonography in our study.

Although some studies showed that central LNM did not affect survival, more and more researches reported regional LNM was associated with increased local recurrence rates and reduced survival. 2.3Current investigations show there are two different varieties of PTMC, tumors with benign biological and clinical courses and those aggressive tumors in terms of lymph node and distant metastasis (Lin et al., 1997; Roti et al., 2006). These aggressive tumors have some characteristics such as larger tumor size, multifocality , extrathyroid invasion and so on. It would be beneficial to identify the subset of patients with PTMC who have aggressive pathological features so that a full treatment protocol could be provided. The aim of this study is to examine the risk factors predictive of subclinical central LNM in patients with PTMC who underwent prophylactic CLND, so we can select aggressive PTMC patients from conventional PTMC patients at diagnosis.

Although women have been shown to be more susceptible to PTC than men, male gender has previously

been suggested as important indicator for LNM in previous reports (Yang et al., 2014). In this study, the CLNM positive rate of males was 59.5%, which, in multivariate analysis, was independently predictive of central compartment LNM (p=0.000).

Generally, central LNM is associated with a larger tumor size. Tumor size (>7or 8mm) has been reported as a predictive factor of subclinical LNM in PTMC patients (Park et al.,2014; Adolfo Pisanu et al., 2014). Our study confirmed that patients with a tumor size≥6mm had a significantly increased risk for central LNM compared to patients with a tumor size <6mm (54%*vs* 24%, p<0.001, OR 6.606). Therefore, tumor size can help in the selection of aggressive PTMC patients.

Studies have shown multifocal PTC may be related to clonal selection from a preneoplastic field and spread throughout the thyroid gland (Jovanovic et al., 2010; Mazeh et al., 2011), which may be linked to central compartment LNM (Zhao et al., 2013). Kim et al. (2013) also demonstrated that multifocaltiy is an independent predictive factor for central LNM. In our study, 32.6% of PTMC patients was found multifocality, and 45.2% of them had central LNM, which , in univariate analysis, was significantly higher than unifocal (p=0.002). This was similar to the results of prior studies, which reported PTMC multifocality was found in 20% to 40% of PTMC patients, 40% to 70% of whom had LNM (Mercante et al.,2009 ; Connor et al., 2011; Dunki-Jacobs et al., 2012). However, in multivariate analysis, there was no significant difference in the rate of CLNM between unifocal and multifocal group (p=0.189).

ECS is traditionally considered to have predictive value for central compartment LNM. Yang et al. (2014) reported tumoral infiltration of thyroid capsule was found in 12.7% of PTC, 78.4% of whom had LNM. Our study showed ECS was found 11.2% of PTMC, 70% of whom had LNM, which was significantly higher than ECS absent group (p=0.005). In multivariate analysis, ECS was an independently risk factor of central compartment LNM (p=0.000).

In conclusion, LNM was common in cN0 PTMC patients and may be predicted by clinical features such as male gender, larger tumor size and ECS. Our findings may help to guide clinicians in the selection of candidates suitable for CLND. Prophylactic CLND may be recommended for these aggressive PTMC patients.

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