

Risk factors analysis of lymph node metastasis in central zone of papillary thyroid microcarcinoma.

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Abstract

Objective: To explore relevant risk factors of lymph node metastasis in central zone of Papillary Thyroid Microcarcinoma (PTMC) in patients, which will provide a certain clinical basis for lymph node dissection surgery in central zone selectively.

Method: Clinical data of 150 PTMC patients (recurrence cases because of surgery were excluded) with surgical treatment in Qilu hospital of Shandong university from October 1st, 2011 to January 30th, 2013. Independent risk factors of lymph node metastasis in central zone were given retrospective analysis.

Results: Total metastasis rate of PTMC in central zone was 35.3% (53/150). Single factors analysis show that size of tumor, whether had envelope invasion, clinical typing cN1 patients had close relations with lymph node metastasis in central zone, $P < 0.05$; multiple factors analysis show that size of tumor (OR=2.466, $P=0.010$), envelope invasion (OR=1.632, $P=0.005$), clinical typing (OR=2.070, $P=0.001$) were independent risk factors of lymph node metastasis in central zone; lymph node metastasis rate in central zone of patients without three independent factors was 16.3%, 7/43, which lower than patients with any one risk factor (43.0%, 45/107) obviously, $P=0.002$.

Conclusion: Size of tumor, tumor invading envelope, clinical typing cN1 are independent risk factors of lymph node metastasis in central zone. Patients who have relevant risk factors should be given lymph node dissection in central zone.

Keywords: Papillary thyroid microcarcinoma (PTMC), Lymph node metastasis, Lymph node dissection in central zone, Retrospective study, Risk factors.

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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 [1]. There has been a substantial rise in the incidence of thyroid cancer in developed countries during the past 30 y [2-4]. Most PTMC grow slowly. The prognosis is better. But it is still has 1% death rate, 5% lymph node metastasis in lateral cervical area and 2.5% long-distance metastasis rate [5]. Cervical lymph node metastasis is risk factor of recurrence and long-distance metastasis [6]. However, in central lymph node dissection of PTMC during surgery, there still has argument at present [7-10]. Therefore, in this retrospective study, 150 PTMC patients were selected in Qilu Hospital of Shandong University, and explore risk factors of lymph node metastasis in central zone, which will provide certain theoretical basis for clinical treatment.

Objects and Methods

Case selection and general data

Inclusive criteria: It cannot touch cervical lymph node examined before surgery; Pathology after surgery diagnosed as PTMC; the age was below 65 y old; blood routine, liver and kidney function, glucose were normal; heart and lung function were normal.

Exclusive criteria: Pathology after surgery was thyroid undifferentiated cancer or medullary thyroid carcinoma; accompanied with other diseases; complications after surgery. 150 PTMC patients with first treatment in Qilu Hospital of Shandong University from October 1st, 2011 to January 30th, 2013 were given surgical treatment. Clinical examination not touches lymph node. Pathology diagnosed after surgery diagnosed as PTMC. In 150 patients, of which, there were 32 male cases and 118 female cases. The age was from 19 to 65 y old. Middle age was 43 y old. Maximum diameter of tumor was from 2 to 10 mm; there were 21 envelope invasion and

129 non-invasion envelope; single onset of primary focus was 98 cases. Lateral multiple onset was 32 cases; patients who accompanied by benign tumor are 60 cases and not are 90 cases; accompanied by TSH was 136 cases, Normal level was 7 cases. Low level was 7 cases; Clinical metastasis typing of cervical lymph node followed clinical evaluation criteria of cervical lymph node by Kowalski et al., which can be divided into cN0 group and cN1 group, there were 130 cases in cN0 group and 20 cases in cN1 group, 34 cases with Hashimoto disease [7]. Surgery followed open thyroid surgery of American thyroid association guidelines by doctors in the same group [8].

Surgical methods

This study decided surgical methods according to report results of rapid freeze pathological slice during surgery and color ultrasound before surgery. 109 patients who had unilateral PTMC were given excision of unhealthy gland lobe and isthmus and lymph node dissection in central zone of unhealthy part; 41 patients with bilateral, isthmus PTMC or unilateral PTMC and multiple benign node in the opposite part given complete excision of thyroid gland, bilateral lymph node dissection in central zone. Dissection range included beside the same lateral trachea, before trachea, lymph node before throat, up to hyoid bone level, down to the upper border of sternum, outside to cephalic artery, front to superficial cervical fascia, backward to deep cervical fascia. Examination before surgery showed there were 48 cases with lymph node metastasis in lateral neck given functional cervical lymph node dissection.

Statistical methods

This study used SPSS 20.0 to do statistical analysis on data. χ^2 test was used to do single factor analysis of relevant factors of lymph node metastasis in central zone, binomial logistic regression to do multiple factor. Detection criteria were $\alpha=0.05$.

Ethical consideration

The study was carried out in compliance with the Declaration of Helsinki of the World Medical Association, and according to a protocol approved by the Ethical Committee of Linqu people's Hospital, the approval number is 2011005. The objectives of the study were explained to the study participants and verbal consent was obtained before interviewing each participant.

Results

Metastasis rate of lymph node in central zone

150 patients, 53 cases were diagnosed as lymph node metastasis in central zone by pathology. Metastasis rate was 35.3%.

Single factor analysis

Table 1 shows that lymph node metastasis in central zone had close relations with whether had envelope invasion, size of

tumor and clinical typing, $P<0.05$; had no relations with age, sex, primary focus number, whether had other thyroid benign diseases, changes of TSH level, whether had Hashimoto etc, $P>0.05$.

Multiple factors analysis

This study took lymph node metastasis as dependent variable, sex, age, size of tumor, envelope invasion, primary focus number, accompanied with benign tumor, TSH, clinical typing, chronic lymph cellular thyroiditis as independent variables to do binomial logistic regression analysis. Results showed that size of tumor (OR=2.466, $P=0.010$), envelope invasion (OR=1.632, $P=0.005$), clinical typing (OR=2.070, $P=0.001$) were independent factors of lymph node metastasis in central zone, seen in Table 2.

Table 1. Single analysis results of clinical pathological parameter and lymph node metastasis in central zone.

Factors	Cases	Metastasis (n (%))	χ^2	P value
Sex				
Male	32	14 (43.8)	1.261	0.261
Female	118	33 (33.1)		
Age (y)				
<45	72	30 (41.7)	2.431	0.119
≥ 45	78	23 (29.5)		
Envelope invasion				
Yes	21	14 (66.7)		
No	129	39 (30.2)	10.492	0.001
Primary focus number				
Single onset	98	30 (31.5)		
Unilateral multiple onset	20	12 (55.0)	3.986	0.136
Bilateral multiple onset	32	11 (34.4)		
With benign diseases				
With	60	17 (28.3)		
Without	90	36 (40.0)	2.145	0.143
TSH				
Normal	136	47 (34.6)		
Increase	7	2 (28.6)	1.633	0.442
Lower	7	4 (57.1)		
Clinical typing				
cN0	130	30 (29.2)		
cN1	20	15 (75.0)	15.891	<0.001
Whether had Hashimoto				
With	34	11 (32.4)		
Without	116	42 (36.2)	0.171	0.679

Size of tumor (cm)				
≤ 0.5	52	11 (21.2)	7.004	0.008
>0.5	98	42 (42.9)		

Table 2. Multiple factors logistic regression analysis results of clinical pathological parameter and lymph node metastasis in central zone.

Factors	B	S.E	Wald	Sig.	OR
Sex	0.435	0.499	0.757	0.384	1.544
Age	0.729	0.417	3.048	0.081	2.072
Size of tumor	2.466	0.953	6.694	0.01	11.773
Envelope invasion	1.632	0.577	7.998	0.005	5.114
Primary focus number	0.067	0.253	0.069	0.793	1.069
Benign tumor	-0.234	0.432	0.293	0.588	0.792
Hashimoto	0.562	0.545	1.061	0.303	1.754
TSH	0.268	0.43	0.388	0.533	1.307
Clinical typing	2.07	0.64	10.463	0.001	7.921
Quantity	-3.712	0.933	15.843	<0.001	0.024

Note: χ^2 test in two groups with or without risk factors.

Metastasis rate of patients without three risk factors was 16.3% (7/43). Metastasis rate of patients with any one risk factor was 43.0% (45/107), there were statistical differences, P=0.002. It showed that metastasis rate of patients without risk factors with lymph node metastasis in central zone lower than patients who had risk factors.

Discussion

Treatment guide of thyroid node and total thyroid cancer in America Thyroid Cancer in 2009 pointed out that patients with lymph node metastasis in central zone and lateral cervical area are given lymph node dissection in central zone. Differentiated thyroid cancer of T3 and T4 are given preventive unilateral or bilateral lymph node dissection in central zone, but unrelated differentiated thyroid cancer of T1 and T2 not given lymph node dissection in central zone [7]. There still have great argument in preventive lymph node dissection in central zone in treating PTMC [3-6]. In long-time follow-up of 535 PTMC patients by Hay et al., it finds that no preventive lymph node dissection can make patients survive without tumor [3]. But there are reports show that lymph metastasis in central zone can influence metastasis and recurrence of patients. Preventive lymph node dissection in central zone can improve prognosis of patients [5,6]. Many scholars in China advocate lymph node dissection, but there are studies show that lymph node dissection cannot reduce recurrence, can increase complications after surgery [9-12]. How to identify who have lymph node metastasis in central zone of PTMC patients and taking it as basis are very important. With the development of technology, high resolution ultrasound improve diagnostic rate of PTMC. But there are 7.0% to 24.4% patients have lymph

node metastasis and recurrence in central zone in cN0 patients according to clinical body examination and iconography examination [13,14]. This study finds that 29.3% cN0 patients have metastasis, which is similar to study results of Wu et al. [15]. There are many potential factors influence lymph node metastasis in central zone, such as sex, age, tumor envelope invasion, multiple tumor, tumor location, with benign tumor, hyperthyroidism and chronic lymph cellular thyroiditis etc. Multiple factors analysis show that size of tumor, tumor envelope invasion and clinical typing are risk factors of lymph node metastasis in central zone. Single factor analysis show that size of tumor, whether have envelope invasion and clinical typing of lymph node metastasis in central zone also influence lymph node metastasis in central zone. With the enlargement of tumor, increase of new vessels, lymph canal, tumor has envelope and extra gland invasion, which will cause invasion of lymph canal and metastasis of lymph node. Invasive molecular mechanism study of thyroid cancer finds that the enlargement of tumor had close relations with BRAF gene mutation. Mutation BRAF gene had close relations with tumor envelope invasion and lymph node metastasis, which also support enlargement of tumor diameter and envelope invasion, causing lymph node metastasis in central zone [16-19].

Conclusion

Size of tumor, tumor envelope invasion and clinical typing cN1 are all risk factors of lymph node metastasis in central zone. This study takes patients with risk factors as CLND important objects, even considers receiving complete excision of thyroid gland, which are benefit for radionuclide therapy; other patients with low risk should be given broaden CLND index, but it still needs close follow-up. It can lower long-distance metastasis rate and recurrence rate of patients effectively, also can reduce unnecessary lymph node dissection in central zone, reducing complications of recurrent laryngeal nerve and parathyroid injury caused by lymph node dissection.

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