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Risk factors analysis of cervical lymph node metastasis of papillary thyroid microcarcinoma.

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Abstract

Objective: To explore risk factors of cervical lymph node metastasis of PTMC.
Methods: Clinical pathological data of 169 PTMC patients in thyroid gland surgery in affiliated hospital of Guizhou medical university from January, 2014 to March, 2016 were given retrospective analysis.
Results: 169 cases were given preventive central compartment lymph node clean, of which, 54 cases (32%) had central compartment lymph metastasis. Multiple factors analysis showed that age (OR=1.512, 95% CI: 1.231-1.795, P<0.05), multifocal tumor (OR=2.912, 95% CI: 2.134-3.702, P<0.05), out of envelope (OR=3.818, 95% CI: 1.716-8.494, P<0.05) were independent factors of central compartment lymph metastasis. 30 cases were given central compartment lymph node and lymph node clean in lateral cervical area, of which, 18 cases had lymph node metastasis in lateral cervical area. Multiple factors analysis showed that tumor out of envelope (OR=3.72, 95% CI: 1.693-4.852, P<0.05) was high risk factor of lymph node metastasis in lateral cervical area. 11 cases (6.5%) had central compartment lymph node and lymph node metastasis in lateral cervical area. Out of envelope (OR=2.578, 95% CI: 2.072-3.211, P<0.05) and multifocal tumor (OR=3.229, 95% CI: 1.530-6.814, P<0.05) were high risk factors of central compartment lymph node and lymph node metastasis in lateral cervical area. The sensitivity and specificity of cervical lymph node B ultrasound with high resolution on central compartment lymph node metastasis were 14.8% and 96.5% respectively, lymph node metastasis in lateral cervical area were 94.4% and 83.3% respectively.
Conclusion: Age, multifocal tumor, extrathyroidal invasion are risk factors of PTMC cervical lymph node metastasis. High frequency neck ultrasound examination could be used as a preoperative assessment approach of PTMC lymph node metastases

Keywords: Thyroid tumor, Lymph node metastasis, Cervical lymph node clean, Risk factors.

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Introduction

Over the last three decades the incidence of thyroid cancer has risen dramatically worldwide [1], tripling in the United States [2] and Australia [3], and rising more than 15 fold in South Korea [4]. Papillary Thyroid Microcarcinoma (PTMC) refers to thyroid papillary carcinoma with tumor diameter equal to or below 1 cm [5]. Most PTMC is found by chance. In recent years, because of high resolution cervical ultrasound diagnosis technology improvement and wide application of pintle puncture technology guided by ultrasound, it finds ratio of PTMC increases gradually every year [6,7]. Studies before [8,9] show that most PTMC is in low risk. But recurrence risk of lymph node metastasis is 3.33 times than patients without lymph node metastasis. This study analysed clinical pathological data of 169 PTMC patients from January, 2014 to March, 2016 in thyroid gland surgery in affiliated hospital of Guizhou medical university retrospectively, PTMC clinical pathological features. Lymph node metastasis is an indicator of PTC recurrence and is directly related to the extent of thyroid cancer surgery. Therefore, the aim of this study was to explore the risk factors of lymph node metastasis in central zone and lateral cervical area, which will provide help for clinical diagnosis and treatment.

Materials and Methods

Patients selection

169 PTMC patients from January, 2014 to March, 2016 in thyroid gland surgery in affiliated hospital of Guizhou medical university were selected. All were first visit. It was demonstrated as PTMC by postoperative pathology, given normalization treatment. This study was approved by scientific research ethics committee of affiliated hospital of Guizhou medical university. The research methods refer to this document [10].

Data collection

Data collection included sex, age, size of tumor (maximum diameter of tumor), whether had multifocality, hashimoto thyroiditis, out of envelope, tumor location, lymph node metastasis in central zone and lateral cervical area, surgical methods, recurrence, long-distance metastasis and survival rate after surgery.

Data collection criteria: age was divided by 45 y old; size of tumor was the maximum diameter of tumor; multifocal tumor meant tumor number more than one; hashimoto thyroiditis was demonstrated by pathology; location of single focal tumor was upper part (upper 1/3 of thyroid gland), middle part (middle 1/3 in gland), lower part (lower 1/3 of gland) and isthmus; out of envelope included first, outside gland invasion in minimum degree (such as encroaching sternothyroid muscle and peripheral soft tissue around thyroid gland); second, it beyond thyroid gland envelope to subcutaneous soft tissue, throat, trachea, esophagus and recurrent laryngeal nerve; third, invasion of prevertebral fascia, carotid artery or mediastinal vessels.

Surgical methods

Surgical methods were excision of unhealthy part of thyroid gland lobe and isthmus, complete excision of thyroid gland, lymph node clean in central zone and lateral cervical area. Lymph node clean area followed thyroid cancer diagnosis guide of thyroid gland node and differentiated type in 2012 [11]. Area of lymph node clean in central zone reached up to thyroid cartilage and down to thymus gland, outside to medial margin of carotid sheath, including pretrachea, lateral trachea, lymph node before throat etc. Area of lymph node clean in lateral cervical area reached up to digastric muscle, down to supraclavicular part, inside division was internal margin of carotid sheath, outside division was anterior border of trapezius, including lymph node and soft tissue in II to IV area, all given preventive lymph node clean in central zone. If lymph node metastasis in lateral cervical area found by B ultrasound before surgery, puncture guided by ultrasound, lymph node clean in lateral cervical area was given during surgery.

Treatment after treatment

Establishing individual achieves on patients after surgery. Patients were given reexamination, thyroid function, thyroid globulin, thyroid globulin antibody, B ultrasound on thyroid gland and cervical lymph node, local monitor, long-distance metastasis and survival conditions in 1, 3, 6, 12 months after surgery.

Statistical management

This study used SPSS 20.0 to do analysis. Quantitative data was described by mean ± standard deviation ($\bar{x} \pm s$). Enumeration data was given frequency. Constituent ratio used χ^2 test. Multiple factors analysis used dichotomy logistic regression of stepwise backwards method. Detection criteria was 0.05, $P<0.05$, there were statistical differences.

Results

Patients' general data

Patients number in this study were 169.The age was from 13 to 75 y old. The average age was 46.0 ± 11.1 y old. There were 76 cases (45%) of 45 y old, 93 cases (55%) equal to or over 45 y old. There were 49 males (29.0%) and 120 females (71.0%). The ratio between male and female was 1:2.45; there were 107 cases with maximum diameter equal to or below 0.5 cm (63.3%) and 62 cases over 0.05cm (36. 7%). In all 169 patients, there were 63 cases (37.3%) with thyroid gland lobe, isthmus and lymph node clean in central zone, 76 cases (45.0%) with complete excision of thyroid gland, isthmus and lymph node clean in central zone, 30 cases (17.7%) with complete excision of thyroid gland, lymph node clean in central zone and lateral cervical area. Pathology after surgery demonstrated there were 54 cases with lymph node metastasis in central zone (54/169). Lymph node metastasis rate in central zone was 32.0%. According to B ultrasound and detection during surgery of cervical lymph node before surgery, 30 cases were given lymph node clean in central zone and lateral cervical area, of which, 7 cases had lymph node metastasis in lateral cervical area, 11 cases had lymph node metastasis in central zone and lateral cervical area, 114 cases had single focal tumor. The rate of tumor in upper, middle, lower and isthmus were 25.4%, 35.1%, 29.8% and 9.7%. The rates of multifocal tumor, Hashimoto thyroiditis, out of envelope were 32.5%, 20.7% and 14.8%.

Risk factors of lymph node metastasis in central zone

169 patients were given preventive lymph node metastasis in central zone, of which, 54 cases (32.0%) had lymph node metastasis in central zone. Single factors analysis showed that age below 45 y old, multifocal tumor, out of envelope were risk factors of lymph node metastasis in central zone (all $P<0.05$). Sex, maximum diameter of tumor (>0.5 cm), hashimoto thyroiditis, tumor location were not risk factors of lymph node metastasis in central zone (all $P>0.05$) (Table 1). Logistic multiple factors analysis showed that age below 45 years old, multifocal tumor, out of envelope were risk factors of lymph node metastasis in central zone (all $P<0.05$) (Table 2).

High risk factors of lymph node metastasis in lateral cervical area

169 patients, of which, 30 cases had lymph node clean in central zone and lateral cervical area, 18 cases had lymph node metastasis in lateral cervical area. Single factors analysis showed that maximum diameter of tumor, out of envelope, multifocal tumor, lymph node metastasis in central zone were risk factors of lymph node metastasis in lateral cervical area (all $P<0.05$) (Table 3); logistic multiple factors analysis showed that only out of envelope was high risk of lymph metastasis in lateral cervical area (Table 4).

High risk factors of lymph node metastasis in central zone and lateral cervical area

169 cases, of which, 30 cases had lymph node clean in central zone and lateral cervical area. 11 cases had lymph node metastasis in central zone and lateral cervical area. Single factor analysis and multiple logistic multiple factors analysis showed that out of envelope, multiple focal tumor were shared high risk factors of lymph node metastasis in central zone and lateral cervical area (all P<0.05) (Tables 5 and 6).

Table 1. *Univariate analysis of risk factors for central cervical lymph node metastases (n (%)).*

Factors	Metastasis (n=54)	Non-metastasis (n=115)	χ^2	P	OR	95% CI
Sex						
Male	14 (25.9)	35 (30.4)	0.363	0.547	0.8	0.387~1.655
Female	40 (74.1)	80 (69.6)				
Age (years old)						
<45	35 (64.8)	41 (35.7)				
≥ 45	19 (35.2)	74 (64.3)	12.628	<0.001	3.325	1.690~6. 539
Maximum diameter of tumor (cm)						
>0.5	35 (64.8)	72 (62.6)	0.077	0.781	1.1	0.561~2.159
≤ 0.5	19 (35.2)	43 (37.4)				
Out of envelope						
Yes	17 (31.5)	8 (7.0)	17.534	<0.001	6. 145	2.450~15.416
No	37 (68.5)	107 (93.0)				
Focal number						
Single focus	24 (44.4)	90 (78.3)	19.141	<0.001	0.222	0.111~0.446
Multiple focus	30 (55.6)	25 (21.7)				
Tumor location						
Upper part	6 (25.0)	23 (25.6)	1.499	0.683	-	-
Middle part	10 (41.7)	30 (33.3)				
Lower part	5 (20.8)	29 (32.2)				
Isthmus	3 (12.5)	8 (8.9)				
Hashimoto thyroiditis						
Yes	11 (20.4)	24 (20.9)	0.006	0.940	0.97	0.436~2.160
No	43 (79.6)	91 (79.1)				

Table 2. *Multivariate logistic analysis of risk factors for central cervical lymph node metastases.*

Variables	B	SE	Wals	df	P	OR	95% CI
Age	1.336	0.386	11.983	1	0.001	1.512	1.231~1.795
Out of envelope	1.230	0.524	5.501	1	0.019	2.912	2.134~3.702
Multifocal tumor	1.340	0.408	10.787	1	0.001	3.818	1.716~8.494
Quantity	-0.740	0.721	1.054	1	0.305	0.477	-

Table 3. *Univariate analysis of risk factors for lateral cervical lymph node metastases (n (%)).*

Factors	Metastasis (n=18)	Non-metastasis (n=151)	χ^2	P	OR	95% CI
Sex						

Male	7 (38.9)	42 (27.8)	0.958	0.328	1.652	0.600~4.545
Female	11 (61.1)	109 (72.2)				
Age (years old)						
<45	9 (50.0)	67 (44.4)	0.206	0.650	1.254	0.471~3.334
≥ 45	9 (50.0)	84 (55.6)				
Maximum diameter of tumor (cm)						
>0.5	16 (88.9)	91 (60.3)	5.673	0.017	5.275	1.170~23.774
≤ 0.5	2 (11.1)	60 (39.7)				
Out of envelope						
yes	13 (72.2)	12 (7.9)	52.713	<0.001	30.117	9.180~98.807
no	5 (27.8)	139 (92.1)				
Focal number						
Single focus	7 (38.9)	107 (70.9)	7.489	0.006	0.262	0.095~0.719
Multiple focus	11 (61.1)	44 (29.1)				
Tumor location						
Upper part	2 (28.6)	27 (25.2)	0.881	0.83	-	-
Middle part	3 (42.8)	37 (34.6)				
Lower part	2 (28.6)	32 (29.9)				
isthmus	0 (0.0)	11 (10.3)				
Lymph node metastasis in central zone						
Yes	11 (61.1)	43 (28.5)	7.878	0.005	3.947	1.436~10.852
No	7 (38.9)	108 (71.5)				
Hashimoto thyroiditis						
Yes	5 (27.8)	30 (19.9)	0.613	0.434	1.551	0.513~4.689
No	13 (72.2)	121 (80.1)				

Table 4. *Multivariate logistic analysis of risk factors for lateral cervical lymph node metastases.*

Variables	B	SE	Wals	df	P	OR	95% CI
Out of envelope	3.405	0.606	31.554	1	<0.001	3.272	1.693~4.852
Quantity	-0.659	0.951	0.480	1	0.488	0.517	-

Table 5. *Univariate analysis of risk factors for concomitant central and lateral cervical lymph node metastases (n (%)).*

Factors	Metastasis (n=11)	Non-metastasis (n=158)	χ^2	P	OR	95% CI
Sex						
Male	3 (27.3)	46 (29.1)	0.017	0.896	0.913	0.232~3.595
Female	8 (72.7)	112 (70.9)				
Age (years old)						
<45	6 (54.5)	70 (44.3)	0.436	0.509	1.509	0.442~5.149
≥ 45	5 (45.5)	88 (55.7)				
Maximum diameter of tumor (cm)						

>0.5	9 (81.8)	98 (62.0)	1.735	0.188	2.755	0.576~13.183
≤ 0.5	2 (18.2)	60 (38.0)				
Out of envelope						
No	9 (81.8)	16 (10.1)	41.934	<0.001	39.938	7.927~201.204
Yes	2 (18.2)	142 (89.9)				
Focal number						
Single focus	2 (18.2)	112 (70.9)	13.012	<0.001	0.091	0.019~0.439
Multiple focus	9 (81.8)	46 (29.1)				
Tumor location						
Upper part	0 (0.0)	29 (25.9)	1.121	0.772	-	-
Middle part	1 (50.0)	39 (34.8)				
Lower part	1 (50.0)	33 (29.5)				
Isthmus	0 (0.0)	11 (9.8)				
Hashimoto thyroiditis						
Yes	3 (27.3)	32 (20.3)	0.309	0.579	1.477	0.371~5.884
No	8 (72.7)	126 (79.7)				

Table 6. *Multivariate logistic analysis of risk factors for concomitant central and lateral cervical lymph node metastases.*

Variables	B	SE	Wals	df	P	OR	95% CI
Out of envelope	1.311	0.504	6. 778	1	0.009	2.578	2.072~3.211
Multiple focal tumor	1.172	0.381	9.466	1	0.002	3.229	1.530~6.814
Quantity	0.038	1.202	0.001	1	0.975	1.039	-

The significance of High resolution lymph node B ultrasound on lymph node metastasis diagnosis in central zone

169 patients, B ultrasound on lymph node metastasis diagnosis doubted that there were 12 cases with lymph node metastasis diagnosis in central zone. Pathological diagnosis was 54 cases. B ultrasound showed there were 4 cases with lymph node metastasis in central zone and diagnosed as negative. 46 cases diagnosed by pathology as positive and B ultrasound as negative. The rate of B ultrasound on lymph node on sensitivity, specificity and false negative rate and false positive rate were 14.8%, 96.5%, 85.2% and 3.5% respectively.

Significance of high resolution cervical lymph node B ultrasound before surgery on lymph node metastasis in lateral cervical area

High resolution cervical lymph node B ultrasound before surgery doubted there were 19 cases with lymph node metastasis in lateral cervical area. Pathological diagnosis was 18 cases. B ultrasound showed that there were 2 cases with lymph node metastasis in lateral cervical zone and diagnosed as negative. There was one negative case diagnosed as positive by pathology and as negative by B ultrasound. The rate of high resolution cervical lymph node B ultrasound on lymph node on sensitivity, specificity and false negative rate and false positive rate were 94.4%, 83.3%, 5.6% and 16.7%.

Disease recovery

169 patients were given 6-moth follow-up. The average follow-up time was 15.8 ± 7.5 months.

There were 7 cases (4.7%) with sudden recurrent laryngeal nerve injury after surgery, 5 cases (3.0%) with temporal hypocalcemia, all recovered within three months. Patients were given reexamination, thyroid function, thyroid globulin, thyroid globulin antibody, B ultrasound on thyroid gland and cervical lymph node, local monitor, long-distance metastasis and survival conditions in 1, 3, 6, 12 months after surgery. There were no patients had recurrence and long-distance metastasis during follow-up, relevant death of patients caused by PTMC.

Discussion

In recent years, incidence rate of thyroid cancer increases gradually. PTMC in thyroid cancer new onset number was over 50% in data by WHO in 2014. PTMC had better prognosis after normalized treatment. The survival rate about 15 y reached up to 99%. Recurrence rate was below 5%. There were 1/3 PTMC had relations with high invasion of tumor. The prognosis was poor [12,13]. In addition, at present, whether PTMC needed surgical treatment and surgical methods, especially lymph node management were still not reached to

consensus. The purpose of this study was to explore high risks of PTMC cervical lymph node metastasis by clinical and pathological features, which will provide theoretical evidence for clinical normalized treatment.

The arguments for PTMC surgical methods at present

There still have argument for excision range of PTMC at present. According to diagnosis guide of thyroid node and differentiated thyroid cancer [11], Excision range of thyroid gland mainly includes nearly or completes excision of thyroid gland, thyroid gland lobe and isthmus. There still have differences on lymph node clean prevention in central zone at home and abroad. America guide points out that non-invasive, no effects on thyroid node of patients, who cannot be given thyroid node clean in central zone, thinking preventive thyroid node clean cannot lower death rate of these patients, increase injury rate of recurrent laryngeal nerve and parathyroid glands [14,15]. Recent studies show that preventive lymph node clean in central zone cannot increase risk of bleeding, permanent hypocalcemia, permanent recurrent laryngeal nerve injury [16], preventive lymph node in central zone in support surgery. Preventive lymph node clean in central zone can improve accuracy of TNM typing of patients and recurrence risk degree, which will be benefit for treatment program after surgery [17]. In this study, there are 8 cases with temporal recurrent laryngeal nerve injury after surgery (4.7%), 5 cases with temporal hypocalcemia (3.0%), all recover to normal level within three months. Because cervical lymph node ultrasound before surgery is not sensitive to whether metastasis happens on lymph node in central zone. In Chinese guide recommend surgery, under conditions of effective recurrent laryngeal nerve and parathyroid gland reservation, whatever size of tumor primary focus, which is given lymph node clean in central zone in the same lateral of focus at least. For patients with doubted lateral lymph node metastasis, it is suggested that functional cervical lymph node clan surgery.

Risk factors of lymph node metastasis in PTMC central zone

PTMC is the main metastasis path for lymph metastasis. Relevant studies [18] show that metastasis rate of lymph node in PTMC central zone is from 24% to 64%. This study includes 169 cases. There are 54 cases with lymph node metastasis in central zone. The rate of lymph node metastasis in central zone is 32.0%, which is similar to document reports [19]. Rate of lymph node metastasis in central zone has obvious relevance with patients' age. Lombardi, Nian et al. [20,21] studies find that lymph node metastasis in the group of age below 45 y old higher than group of age equal to or over 45 y old. This study finds that lymph node metastasis of patients who under 45 y old is 64.8%, equal to or over 45 years old is 35.2%, there are statistical differences ($P<0.01$). Siddiqui et al. found that patients who were <45 y of age were significantly more likely to have central lymph node metastasis [22]. This is consistent with our results. Multifocal tumor is one of PTMC invasive characteristics. Many studies [23,24] show multifocal tumor is independent risk factor of PTMC lymph node metastasis in central zone. Lymph node metastasis rate of patients with thyroid tumor out of envelope higher than patients without envelope invasion (68.0% *vs.* 25.7%, $P<0.001$). So et al. [25] find that lymph node metastasis rate of patients with tumor invading envelope higher than without tumor invading envelope in 551 PTMMC patients.

Single factor analysis showed that age below 45 y old, multifocal tumor, out of envelope are risk factors of lymph node metastasis in central zone ($P<0.05$). Logistic multiple factors show that age below 45 y old (OR=1.512, 95% CI: 1.231-1.795, $P<0.05$), multifocal tumor (OR=2.912, 95% CI: 2.134-3.702, $P<0.05$), out of envelope (OR=3.818, 95% CI: 1.716-8.494, $P<0.05$) are high risk factors of lymph node metastasis in central zone. In this study, male and maximum diameter of tumor are not risk factors of lymph node metastasis in central zone, which form contrast with these studies at present [23,26]. Considering this study is PTMC or small sample.

Risk factors of lymph node metastasis in PTMC lateral cervical zone

Some studies [18] point out of envelope, multifocal tumor, lymph node metastasis in central zone are risk factors of lymph node metastasis in lateral cervical area. Some other scholars [27] point out tumor locating in upper part, out of envelope, calcium, lymph node metastasis in central zone are risk factors of lymph node metastasis in lateral cervical area. Some scholars studies [28,29] show that lymph node metastasis in lateral cervical area comes from lymph node metastasis in central zone. Number of lymph node metastasis in central zone has positive relations with lymph node metastasis in lateral cervical area. When there are 3 to 5 lymph node metastases in central zones, the rate of lymph node metastasis in lateral cervical area will reach up to 50% to 80%. When there is no lymph node metastasis in central zone, the rate of lymph node metastasis in lateral cervical area will lower than that of 20%. Single analysis in this study finds that maximum diameter of tumor, multifocal tumor, out of envelope, lymph node metastasis in central zone are risk factors of lymph node metastasis in lateral cervical area. Logistic multiple factors analysis showed that tumor invading thyroid envelope (OR=3.72, 95% CI: 1.693-4.852, $P<0.05$) is independent risk factor of lymph node metastasis in lateral cervical area.

Risk factors of lymph node metastasis in central zone and lateral cervical area of PTMC

Multifocal tumor forms may be caused by selective clone of multifocal precancerous lesions, then spreading to whole thyroid gland. During this process, it will cause lymph node metastasis. Lymph node metastasis of mutlifocal tumor risk increases 17.9 times comparing with single focus tumor metastasis risk [20]. Tumor invading out of thyroid envelope is one of invasive PTMC. Under stimulation of some genes of invasive tumor, thyroid extracellular matrix lost restriction for

thyroid cancer metastasis, which will cause tumor metastasis [30].

Zheng et al. [31] think that PTMC and HT are independent risk factors of lymph node metastasis in lateral cervical area, lateral cervical area and central zone. This study finds that out of envelope (OR=2.578, 95% CI: 2.072-3.211, P<0.05) and multifocal tumor (OR=3.229, 95% CI: 1.530-6.814, P<0.05) are high risk factors of lymph node metastasis in central zone and lateral cervical area.

The significance of high resolution cervical lymph node B ultrasound before surgery on lymph node metastasis of thyroid cancer

Cervical lymph node ultrasound has become the first iconography method for evaluating lymph node quality.

70 of migration thyroid papillary cancer relate to central zone and lymph node in lateral cervical area [32]. For patients diagnosed or doubted as thyroid cancer, who are given cervical lymph node B ultrasound, the purpose is to identify lymph node in central zone and lateral cervical are, which needs surgical excision [33,34]. Ultrasound finds that the specificity of lymph node metastasis of thyroid papillary cancer is very high. Detection in central zone and lateral cervical area are up to 80% to 95% [35]. This study finds that sensitivity and specificity of cervical lymph node B ultrasound on lymph node metastasis in central zone were 14.8% and 96.5% respectively. Its sensitivity and specificity on lymph node metastasis in lateral cervical zone are 94.4% and 83.3% respectively. The detection specificity of lymph node metastasis is high. The sensitivity of lymph node metastasis diagnosis in lateral area is high. Therefore, High resolution cervical lymph node B ultrasound can be important method for evaluating lymph node metastasis of thyroid cancer before surgery.

Above all, this study shows that age below 45 y old, multifocal tumor, out of envelope are risk factors of lymph node metastasis in central zone. Tumor invading out of envelope is independent factor of lymph node metastasis in lateral cervical area. Out of envelope, multifocal tumor is risk factor of lymph node metastasis in central zone and lateral cervical area. High resolution cervical lymph node B ultrasound can be important method for evaluating lymph node metastasis of thyroid cancer before surgery. This study thinks under effective recurrent laryngeal nerve and parathyroid of PTMC patients, it should be given lymph node clean in central zone, which can avoid increased risk of parathyroid and recurrent laryngeal nerve injury caused by scar cohesion of surgery again and anatomic unclear location.

For patients who are doubted as lymph node metastasis in lateral cervical area, it should be given normalized functional clean surgery of cervical lymph. According to evaluation after surgery, given selective iodine 131 treatment. 169 patients in this study are given 6-month follow-up at least. The average follow-up time was 15.9 (6 to 32 months). Recurrence number during follow-up is 0. Short-time follow-up is the limitation of this paper for predicting recurrence. At the same time, this study not classifies and discusses pathological subtypes of PTMC which will influence study results and it is the limitation of this study.

Several limitations of this study should be considered. Firstly, this research was a cross-sectional study; the mechanism involved in the interactive effect is still unclear. Further studies are needed to unravel this. Secondly, the sample size is not big enough. However, the study setting is a modern, high level comprehensive medical institution with sophisticated clinical diagnosis facilities and medical record management. Thus, the data used can be deemed reliable.

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