Original paper

Risk factors for central lymph node metastasis in papillary thyroid microcarcinoma – a retrospective study of 1433 cases from a single center

Yaoyuan Shen, Wenjing Pu, Hongrun Zhou, Mei Cui, Wei Zhao, Jin Ma, Chun Wang, Zhenzhu Sun

People's Hospital of Xinjiang Uygur Autonomous Region
Yaoyuan Shen and Wenjing Pu contributed equally to this work.

The purpose of this retrospective study was to evaluate the clinicopathological features of papillary thyroid microcarcinoma (PTMC) and the lymph node metastasis of PTMC.

We retrospectively reviewed a total of 1433 patients with PTMC. The analysis data including demographics, tumor size, multifocality, bilateral, invasion capsule and Hashimoto's thyroiditis were collected from XinJiang, China.

Univariate and multivariate analyses were performed to identify the clinicopathologic predictors of central lymph node metastasis: male gender [odds ratio (OR) = 2.358, $p < 0.001$], age ≤ 45 years (OR = 2.302, $p < 0.001$), sum of tumor size > 6.5 mm (OR = 2.388, $p < 0.001$), adjacent or invasion capsule (OR = 1.750, $p = 0.002$), Hashimoto's thyroiditis (OR = 0.501, $p < 0.001$). The optimal critical value of the number of dissected lymph nodes was found to be 8.5 using ROC analysis, with a sensitivity and specificity of 41.8% and 75.5%, respectively.

This study suggests that evaluation of nodal metastasis is required to guide the surgical treatment of PTMC patients.

Key words: PTMC, risk factors, central lymph node, papillary thyroid microcarcinoma.

Introduction

The prevalence of thyroid carcinoma has significantly increased in recent years [1]. In particular, the prevalence of papillary thyroid microcarcinoma (PTMC) has increased faster than other types of papillary thyroid cancers (PTCs). The 2014 World Cancer Report stated that over 50% were PTMCs among the new cases of thyroid carcinoma [2]. The reasons why the number of PTMCs is increasing include increased examination opportunities for the thyroid gland, and thyroid ultrasonography (US) and fine-needle aspiration cytology, which can easily diagnose PTMC, are widely used [3, 4]. However, the management of PTMC remains controversial. The practice in thyroid pathology has many differences between Asian and Western countries [5, 6]. An important debate is the need for prophylactic central lymph node dissection in patients with PTMC. Routine prophylactic central neck dissection may result in recurrent laryngeal nerve injury and hypoparathyroidism in some patients without lymph node metastasis. Conversely, simple thyroidectomy may cause high risk for metastatic lymph nodes. Current thyroid nodule ablation therapy results in the same dilemma [7]. Therefore, it is necessary to identify the predictive factors for lymph node metastases in patients with PTMC and to perform prophylactic lymph node dissections in high-risk patients with selectivity.

There are a few large data studies that have explored the clinicopathological factors and biological behavior of PTMC. Central lymph node metastasis (CLNM) has been considered as a poor prognostic factor for local recurrence and survival [8, 9] in patients with PTMC. In addition, many clinical and imaging methods have been used to identify benign and malignant nodules of the thyroid gland but with limited practicality. For example, the sensitivity of US for detecting CLNM was very low [10] because of its limited resolution. The aim of this retrospective study is to explore the clinicopathological features of PTMC and risk factors of lymph node metastasis in patients with PTMC.

Materials and methods

General clinical materials

This retrospective study was approved by the Institutional Review Board of People's Hospital of Xinjiang Uygur Autonomous Region, and all patients signed informed consent forms or they were waived.

Patient selection

A total of 3073 patients with thyroid carcinoma were hospitalized in People's Hospital of Xinjiang Uygur Autonomous Region from January 1st, 2008 to December 31st, 2020. Of those, the current study included 1433 patients with non-high-risk PTMC who underwent surgical resection in this study. None of the patients had received preoperative chemoradiotherapy or other neoadjuvant therapy. The diameter of the tumor was in the range 1–10 mm, and all patients have undergone bilateral thyroidectomy and prophylactic central lymph node dissection. Clinical and pathological data including gender, age at diagnosis, tumor largest diameter, capsular invasion, multifocal, bilateral, combined Hashimoto's thyroiditis, number of dissected lymph nodes and CLNM of all the cases were collected and checked by two pathologists.

Statistical methods

SPSS 26.0 software was used to conduct all the statistical analysis. Counting data were compared by χ^2 test. Receiver-operating characteristic (ROC) analysis was used to identify the cut-off point of the sum of the largest diameter of multifocal tumors. Age and number of dissected lymph nodes were selected as the dependent variables for defining the risk of CLNM and CLNM with metastasis. Logistic analysis was used to analyze the factors affecting the occurrence of metastasis in patients. $P < 0.05$ was considered statistically significant.

Results

Clinicopathological characteristics of papillary thyroid microcarcinoma

A total of 1433 patients with PTMC who underwent conventional open surgery were included in this study. The clinicopathological characteristics of the study population are summarized in Table 1.

Number of cases and sex ratio

The number of cases per year for men and women is shown in Figure 1. The incidence tendency of the men and women was not significantly different ($p > 0.05$), and the highest number of cases occurred in women at age 47, men at age 43.

Tumor size

Of the 1433 cases, 940 patients had unifocal carcinoma. The average largest tumor diameter of the 940 was 5.6 ±0.08 mm. Of those, 449 (47.8%) and 491 (52.2%) patients' average largest tumor diameter was 5 mm or smaller and larger than 5 mm, respectively. The tumor is considered to be multifocal when more than one focus was found in bilateral or unilateral thyroid gland lobes. As a result, 493 patients were multifocal in this study. The maximum diameter was defined as the sum of the diameters of all lesions. The diameter of tumors was calculated by the sum of diameters of multiple lesions. The average largest tumor diameter of the 493 cases was 11.8 ±0.7 mm.

Risk factors of central lymph node metastasis

Central lymph node metastasis was present in 498 (34.8%) patients. First, we studied the relationship between these risk factors and CLNM. The optimal critical value of the tumor diameter was found to be 7.5 mm in patients with CLNM using ROC analysis, with a sensitivity of 54.7% and a specificity of 66.3%. The optimal critical value of age was found to be 45.5 years in patients with LNM using ROC analysis, with a sensitivity of 59% and a specificity of 61.50%. The optimal critical value of the number of dissected lymph nodes was found to be 8.5 in patients with CLNM using ROC analysis, with a sensitivity of 41.8% and a specificity of 75.5%. The results of univariate analysis showed that LNM was significantly associated with age, gender, tumor largest diameter, capsular invasion, multifocality, bilateral, combined Hashimoto's thyroiditis, and number of dissected lymph nodes. The results of multivariate analysis showed that LNM was significantly associated with age, gender, tumor largest diameter, capsular invasion, combined Hashimoto's thyroiditis, and number of dissected lymph nodes (Table II).

Table I. Clinicopathological characteristics of all enrolled patients

Characteristics	No	%	CLNM			
			Yes		No	
			No.	%	No.	%
Gender						
Male	319	22.30	169	53	150	47
Female	1114	77.70	329	29.50	785	70.50
Age (years)						
Median (range)	46.27 ±0.25(13–75)					
10–20	4	0.30	4	100	0	0
21–30	76	5.30	46	60.50	30	39.50
31–40	295	20.60	144	48.80	151	51.20
41–50	587	41	188	32	399	68
51–60	387	27	101	26.10	286	73.90
61–70	78	5.40	14	17.90	64	82
71–80	6	0.40	1	16.70	5	83.30
Sum of tumor maximum diameters (cm)						
Median (range)	0.74 ±0.01(0.1–3)					
≤ 0.7	845	59.0	225	26.60	620	73.40
> 0.7	588	41.0	273	46.40	315	53.60
Unifocal	940	65.6	283	30.10	657	69.90
Multifocality	493	34.40	215	43.60	278	56.40
Unilateral	1085	75.71	339	31.24	746	68.76
Bilateral	348	24.29	159	45.69	189	54.31
Capsular invasion						
Far from the capsule	833	58.10	245	29.40	588	70.60
Adjacent to capsule (≤ 1 mm)	118	8.20	46	39	72	61
Invasion of the capsule but no breakthrough	348	24.30	138	39.70	210	60.30
Break through the capsule to the surrounding tissue	134	9.40	69	51.50	65	48.50
Lymph node metastasis						
Yes	498	34.75				
No	935	65.25				
Hashimoto's thyroiditis						
Yes	183	12.80	41	22.40	142	77.60
No	1250	87.20	457	36.60	793	63.40
Number of dissected lymph nodes						
Median (range)	7.6 ±0.19 (1–70)					
1–10	1123	78.37	344	30.63	779	69.37
11–20	236	16.47	104	44.07	132	55.93
21–30	50	3.49	29	58	21	42
31–40	16	1.11	13	81.25	3	18.75
> 40	8	0.56	8	100	0	0

CLNM – central lymph node metastasis

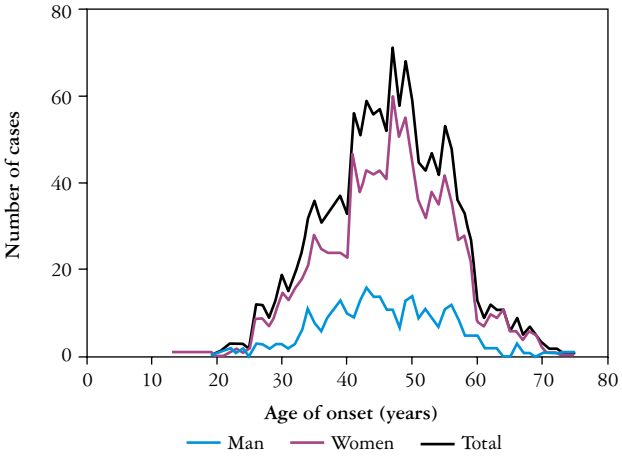

Fig. 1. The number of cases per year for men and women

Discussion

In this retrospective study, we analyzed clinicopathological features of 1433 patients with PTMC and evaluated the risk factors for CLNM. Similar to that in previous studies, the incidence rate of central LNM in patients with PTMC was approximately 23–48.29% [11–14], and the prevalence of CLNM in the present study was 34.8%.

Age is a very important index in the American Joint Committee on Cancer (AJCC) tumor, lymph node, metastasis staging system for thyroid carcinoma. Previous studies indicated that age was a risk factor for CLNM in patients with PTMC [15, 16]. One study showed that age≥45 years was associated with a higher risk of LNM [17]. Conversely, several studies have revealed that younger age was a risk factor for LNM. Luo *et al*. [18] conducted a study including 1031 patients with PTMC. They reported that people aged ≤ 40 years were prone to CLNM. Yin *et al*. [19] retrospectively reviewed 1092 patients with PTMC and found that age < 45 years was an independent predictor of CLNM. The results of our study showed that age ≤ 45 years was an independent risk factor for CLNM in patients with PTMC.

In our study, like the previous studies, the incidence of PTMC in women was much higher than in men, but the rate of lymph node metastases was lower than in men [20]. The rate of lymph node metastasis in men aged ≤ 45 was 59.1%. This phenomenon may have to do with hormonal differences between men and women, with women having higher levels of progesterone and estrogen [21]. However, its complex molecular mechanism is still unclear.

Most studies have shown that multifocality in thyroid cancer was an independent risk factor for lymph node metastases in patients with PTMC [18, 22, 23]. A few studies have shown that central lymphatic metastasis was not associated with multifocality [24]. The results of our study indicated that multifocality was not a risk factor for CLNM metastasis according to the multivariate analysis. We speculated that these findings may related to the redefinition of the maximum diameter of multifocal cases in the current study. We disagreed with the previous researchers, preferring to choose the biggest lesion diameter of tumors to represent the maximum diameter of a multifocal lesion. The ROC analysis showed that the optimal point was 7.5 mm of the sum of the maximum diameter of multifocal lesions, with a sensitivity of 54.7% and a specificity of 66.3%. In the group with the sum of the maximum diameter > 7 mm, the rate of CLNM was 46.43%. Therefore, the sum of the maximum diameter was larger than 7 mm for patients with PTMC. Thus, we have the same opinion as Luo *et al*. [18] that more attention should be paid to CLNM.

The largest diameter of PTMC should be measured as 10 mm or less. It is debatable whether the definition of PTMC should be modified so that the sum of the maximum diameters is measured as 10 mm or less. It has aroused widespread debate since the eighth edition of the AJCC used the intraoperative findings (gross extrathyroidal extension (ETE)) instead of using histopathological examinations (minimal ETE) [25]. Various researchers have put forward different viewpoints. They believed that minimal ETE can increase the risk of tumor recurrence [26–28]. Some studies have reported that thyroid capsular invasion was an independent risk factor for lymph node metastases [29, 30]. However, we found that not only tumor invasion of the capsule, but also the adjacent capsule (< 1 mm) of the tumor were risk factors for lymph node metastasis. However, accurate diagnosis of PTMC is challenging because of the thyroid gland lacking a well-defined true capsule and being composed of thin fibrous tissue which is not obvious. Nevertheless, we believe that the eighth edition of the AJCC underestimates the importance of capsular invasion.

Some researchers have reported that lymphocytic thyroiditis was an independent protective factor for lymph node metastasis, and the lymph node cancer metastasis rate of patients with lymphocytic thyroiditis was lower than that of those without [31, 32]. In our study, we found that combined Hashimoto was an independent protective factor for CLNM. Many previous studies have suggested that this may be related to the HT induced autoimmunity thyroid specific antigen ability to kill tumor cells [33], especially in patients with TPOAb+ [34]. However, others argued its adverse effects on PTC prognosis, especially on CLNM [35, 36]. Therefore, the relationship between PTC and HT remains controversial.

Adequate lymph node dissection/examination is necessary for staging in patients with high risk factors, as the invaded lymph nodes have less chance to be missed. On the other hand, node dissection will

Table II. Univariate and multivariate analyses of central lymph node metastasis, and clinicopathological characteristics of papillary thyroid microcarcinoma

Risk factors	CLNM			Univariate analysis		Multivariate analysis	
	Total (N = 1433)	Yes (n = 498)	No (n = 935)	OR (95% CI)	p	OR (95% CI)	p
Gender, *n* (%)					< 0.001*		< 0.001*
Female	1114 (77.7)	329 (66.1)	785 (84)	1		1	
Male	319 (22.3)	169 (33.9)	150 (16)	2.688 (2.084–3.468)		2.358 (1.799–3.092)	
Age, *n* (%)					< 0.001*		< 0.001*
> 45	779 (54.4)	304 (61.04	754 (80.64	1		1	
≤ 45	654 (45.6)	194 (38.96	181 (19.36	2.302 (1.844–2.874)		2.383 (1.885–3.012)	
Sum of tumor maximum diameters [cm]					< 0.001*		< 0.001*
≤ 0.7	845 (59.0)	373 (74.90	823 (88.02	1		1	
> 0.7	588 (41.0)	125 (25.10)	112 (11.98	2.388 (1.912–2.983)		1.953 (1.489–2.562)	
Adjacent or invasion capsule					< 0.001*		0.002*
Negative	833 (58.13)	245 (49.20)	588 (62.89)	1		1	
Positive	600 (41.87)	253 (50.80)	347 (37.11)	1.750 (1.404–2.181)		1.472 (1.158–1.871)	
Multifocality					< 0.001*		0.96
Negative	940 (65.6)	283 (56.)	657 (70.)	1		1	
Positive	493 (34.4)	215 (43.)	278 (29.)	1.795 (1.432–2.251)		0.989 (0.656–1.492)	
Bilateral					< 0.001*		0.349
Negative	1085 (75.7)	339 (68.)	746 (79.)	1		1	
Positive	348 (24.3)	159 (31.)	189 (20.)	1.851 (1.446–2.370)		1.289 (0.847–1.963)	
Hashimoto's thyroiditis					< 0.001*		0.03*
Negative	1250 (87.2)	457 (91.)	793 (84.)	1		1	
Positive	183 (12.8)	41 (8.2)	142 (15.)	0.501 (0.347–0.722)		0.559 (0.379–0.824)	
Number of dissected lymph nodes					< 0.001*		
≤ 8	1062 (74.1	316 (63.5)	746 (79.8)	1			
> 8	371 (25.9	182 (36.5)	189 (20.2)	2.273 (178.4–2.897)			

CLNM – central lymph node metastasis

reduce the immune activity in the affected region because of the role of lymph nodes in the immune system. Thus, balancing diagnostic accuracy and life quality is critical. However, the reasons for the heterogeneity in lymph node sampling may include the surgical competence and/or pathologist related variables. But in a variety of tumors, quantification of lymph nodes has been studied extensively [37–39]. However, few recommendations [40] have been made for the number of lymph nodes in the thyroid.

Based on our data, our recommended value for the number of lymph nodes for dissection in the at-risk population is a cut-off value of 9. However, more work with larger sample sizes and more detailed analysis is required.

Conclusions

We considered that prophylactic central lymph node dissection should be performed in patients with risk factors of male sex, age ≤ 45 years, sum of tumor size > 7 mm, tumor invasion of the capsule or adjacent capsule (< 1 mm) of the tumor. The number of dissected lymph nodes in high-risk patients is not less than 9. The risk of lymph node metastasis is low in the case of female sex, age > 45 years, sum of tumor size ≤ 0.7, tumor far from the capsular and combined Hashimoto disease. Therefore, evaluation of nodal metastasis is required to guide the surgical treatment of PTMC patients. This study has a major limitation for it did not include molecular analysis of enrolled patients. Future research is needed to investigate the significance of these factors.

The authors declare no conflicts of interest.

References

1. Jung CK, Little MP, Lubin JH, et al. The increase in thyroid cancer incidence during the last four decades is accompanied by a high frequency of BRAF mutations and a sharp increase in RAS mutations. J Clin Endocrinol Metab 2014; 99: E276-E285.
2. Tuttle RM, Haddad RI, Ball DW, et al. Thyroid carcinoma, version 2.2014. J Natl Compr Canc Netw 2014; 12: 1671-1680.
3. Du L, Wang Y, Sun X, et al. Thyroid cancer: trends in incidence, mortality and clinical-pathological patterns in Zhejiang Province, Southeast China[J]. BMC Cancer, 2018,18(1):291.
4. Dal Maso L, Panato C, Franceschi S, et al. The impact of overdiagnosis on thyroid cancer epidemic in Italy,1998–2012[J]. Eur J Cancer 2018; 94: 6-15.
5. Kakudo K. Asian and Western practice in thyroid pathology: similarities and differences. Gland Surg 2020; 9: 1614-1627.
6. Gao M, Ge M, Ji Q, et al. Chinese expert consensus and guidelines for the diagnosis and treatment of papillary thyroid microcarcinoma. Cancer Biol Med 2017; 14: 203-211.
7. Grant CS. Recurrence of papillary thyroid cancer after optimized surgery. Gland Surg 2015; 4: 52-62.
8. Ito Y, Onoda N, Okamoto T. The revised clinical practice guidelines on the management of thyroid tumors by the Japan Associations of Endocrine Surgeons: core questions and recommendations for treatments of thyroid cancer. Endocr J 2020; 67: 669-717.
9. Lee J, Song Y, Soh EY. Central lymph node metastasis is an important prognostic factor in patients with papillary thyroid microcarcinoma. J Korean Med Sci 2014; 29: 48-52.
10. Hwang HS, Orloff LA. Efficacy of preoperative neck ultrasound in the detection of cervical lymph node metastasis from thyroid cancer. Laryngoscope 2011; 121: 487-491.
11. Liu LS, Liang J, Li JH, et al. The incidence and risk factors for central lymph node metastasis in cN0 papillary thyroid microcarcinoma: a meta-analysis. Eur Arch Otorhinolaryngol 2017; 274: 1327-1338.
12. Song J, Yan T, Qiu W, et al. Clinical analysis of risk factors for cervical lymph node metastasis in papillary thyroid microcarcinoma: a retrospective study of 3686 patients. Cancer Manag Res 2020; 12: 2523-2530.
13. Wang Y, Guan Q, Xiang J. Nomogram for predicting central lymph node metastasis in papillary thyroid microcarcinoma: a retrospective cohort study of 8668 patients. Int J Surg 2018; 55: 98-102.
14. Wang ZH, Zhang YJ, Fu GM, et al. [Analysis of risk factors for central lymph node metastasis in papillary thyroid microcarcinoma]. Zhonghua Er Bi Yan Hou Tou Jing Wai Ke Za Zhi 2019; 54: 12-17.
15. Feng JW, Pan H, Wang L, et al. Determine the optimal extent of thyroidectomy and lymphadenectomy for patients with papillary thyroid microcarcinoma. Front Endocrinol (Lausanne) 2019; 10: 363.
16. Xu Y, Xu L, Wang J. Clinical predictors of lymph node metastasis and survival rate in papillary thyroid microcarcinoma: analysis of 3607 patients at a single institution. J Surg Res 2018; 221: 128-134.
17. Jeon MJ, Kim WG, Choi YM, et al. Features predictive of distant metastasis in papillary thyroid microcarcinomas. Thyroid 2016; 26: 161-168.
18. Luo Y, Zhao Y, Chen K, et al. Clinical analysis of cervical lymph node metastasis risk factors in patients with papillary thyroid microcarcinoma. J Endocrinol Invest 2019; 42: 227-236.
19. Yin X, Liu C, Guo Y, et al. Influence of tumor extent on central lymph node metastasis in solitary papillary thyroid microcarcinomas: a retrospective study of 1092 patients. World J Surg Oncol 2017; 15: 133.
20. 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.
21. Rahbari R, Zhang L, Kebebew E. Thyroid cancer gender disparity. Future Oncol 2010; 6: 1771-1779.
22. Gui CY, Qiu SL, Peng ZH, et al. Clinical and pathologic predictors of central lymph node metastasis in papillary thyroid microcarcinoma: a retrospective cohort study. J Endocrinol Invest 2018; 41: 403-409.
23. Xu Y, Xu L, Wang J. Clinical predictors of lymph node metastasis and survival rate in papillary thyroid microcarcinoma: analysis of 3607 patients at a single institution. J Surg Res 2018; 221: 128-134.
24. Zhou YL, Gao EL, Zhang W, et al. Factors predictive of papillary thyroid micro-carcinoma with bilateral involvement and central lymph node metastasis: a retrospective study. World J Surg Oncol 2012; 10: 67.
25. Turk AT, Asa SL, Baloch ZW, et al. Interobserver variability in the histopathologic assessment of extrathyroidal extension of well differentiated thyroid carcinoma supports the New American Joint Committee on cancer eighth edition criteria for tumor staging. Thyroid 2019; 29: 619-624.
26. Tran B, Roshan D, Abraham E, et al. An analysis of the American Joint Committee on cancer 8th edition T staging system for papillary thyroid carcinoma. J Clin Endocrinol Metab 2018; 103: 2199-2206.
27. Yin DT, Yu K, Lu RQ, et al. Prognostic impact of minimal extrathyroidal extension in papillary thyroid carcinoma. Medicine (Baltimore) 2016; 95: e5794.
28. Diker-Cohen T, Hirsch D, Shimon I, et al. Impact of minimal extra-thyroid extension in differentiated thyroid cancer: systematic review and meta-analysis. J Clin Endocrinol Metab 2018.
29. Song J, Yan T, Qiu W, et al. Clinical analysis of risk factors for cervical lymph node metastasis in papillary thyroid microcarcinoma: a retrospective study of 3686 patients[J]. Cancer Manag Res 2020; 12: 2523-2530.

30. Wang W, Gu J, Shang J, et al. Correlation analysis on central lymph node metastasis in 276 patients with cN0 papillary thyroid carcinoma. Int J Clin Exp Pathol 2013; 6: 510-515.
31. Kim SK, Woo JW, Lee JH, et al. Chronic lymphocytic thyroiditis and BRAF V600E in papillary thyroid carcinoma. Endocr Relat Cancer 2016; 23: 27-34.
32. Lang BH, Chai YJ, Cowling BJ, et al. Is BRAFV600E mutation a marker for central nodal metastasis in small papillary thyroid carcinoma? Endocr Relat Cancer 2014; 21: 285-295.
33. Kim SS, Lee BJ, Lee JC, et al. Preoperative ultrasonographic tumor characteristics as a predictive factor of tumor stage in papillary thyroid carcinoma. Head Neck 2011; 33: 1719-1726.
34. Wen X, Wang B, Jin Q, et al. Thyroid antibody status is associated with central lymph node metastases in papillary thyroid carcinoma patients with hashimoto's thyroiditis. Ann Surg Oncol 2019; 26: 1751-1758.
35. Shen CT, Zhang XY, Qiu ZL, et al. Thyroid autoimmune antibodies in patients with papillary thyroid carcinoma: a double-edged sword? Endocrine 2017; 58: 176-183.
36. Iliadou PK, Effraimidis G, Konstantinos M, et al. Chronic lymphocytic thyroiditis is associated with invasive characteristics of differentiated thyroid carcinoma in children and adolescents. Eur J Endocrinol 2016; 174: X1.
37. Sun L, Li P, Ren H, et al. Quantifying the number of lymph nodes for examination in breast cancer. J Int Med Res 2020; 48: 1219679146.
38. Sun L, Liu Q, Ren H, et al. Nodes staging score to quantify lymph nodes for examination in gastric cancer. Medicine (Baltimore) 2020; 99: e21085.
39. Ma D, Zhao S, Huang Y, et al. STARD: how many lymph nodals needed to be dissected in corpus carcinoma? Medicine (Baltimore) 2018; 97: e260.
40. Robinson TJ, Thomas S, Dinan MA, et al. How many lymph nodes are enough? Assessing the adequacy of lymph node yield for papillary thyroid cancer. J Clin Oncol 2016; 34: 3434-3439.

Address for correspondence

Yaoyuan Shen
People's Hospital of Xinjiang
Uygur Autonomous Region
Xinjiang, China
e-mail: shenhuanhuanzg@126.com