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Original contribution

Clinicopathological features and lymph node metastasis risk in early gastric cancer with WHO criteria in China: 304 cases analysis

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ABSTRACT

Aims: The aim of this research was to identify the clinicopathological characteristics of early gastric cancer (EGC) based on the WHO criteria, and to analyze predictors for lymph node metastasis (LNM) in EGC in a Chinese study population.

Methods: We retrospectively collected data of 304 Chinese EGC patients, including 265 patients undergoing radical gastrectomy and 39 patients undergoing endoscopic resection. Histological features were accessed by three experienced pathologists. Univariate analysis and multivariate analysis were used to identify the correlation between clinicopathological features and LNM.

Results: Among the 304 cases with EGC, the rate of well differentiated tubular adenocarcinoma was 11.2%, significantly lower than that of Japanese and South Korean, which was 24.8% and 19.9% respectively ($p<0.001$ and $p = 0.006$), but similar to that of a Western result, which was 11.9% ($p = 0.860$). Among the 265 patients who underwent gastrectomy, 18.5% of the patients had LNM. Univariate analysis showed that macroscopic type, differentiation degree, invasion depth, infiltration pattern (INF), lymphovascular invasion and ulceration were related to LNM. Multivariate analysis revealed that lymphovascular invasion ($p < 0.001$, OR = 6.549), ulceration ($p = 0.035$, OR = 2.527) and INF c ($p = 0.042$, OR = 3.424) were the independent risk factors of LNM in EGC.

Conclusions: The pathological diagnosis standard of well differentiated tubular adenocarcinoma in China significantly differs from that in Japan and South Korea, but is similar to western countries. LNM is more likely to occur in EGCs with lymphovascular invasion, ulceration and INF c.

1. Introduction

Gastric cancer is one of the most common malignancies in China. Over 80% of the gastric cancers have already been in advanced stage when diagnosed, reflecting the low detection rate of early gastric cancer (EGC) [1]. In Japan and South Korea, the detection rates of EGC are 70% and 50% respectively, much higher than that in China. The five-year survival rate in EGC patients is usually more than 90% while that in advanced gastric cancer patients is less than 30% [1,2]. EGC is defined as gastric cancer limited to mucosa or submucosa (pT1) regardless of presence or absence of lymph node metastasis (LNM) [3]. Radical gastrectomy combined with lymph node dissection is commonly considered to be the first choice for treatment. However, in recent years, endoscopic submucosal dissection (ESD) and endoscopic mucosal resection (EMR), alternatives of gastrectomy in some cases, have been widely accepted on account of the same curative effect but smaller trauma, fewer complications and faster recovery. The accurate early prediction of LNM is crucial for endoscopic resection which requires the extremely low risk of LNM [2,4,5]. The Japanese, South Korean and Chinese guidelines for EMR/ESD for EGC are all based on the assessment of LNM risk [1,5-7].

Japanese and South Korean made great contributions to researches on EGC, but their diagnostic criteria for EGC are quite different from those made by Western counterparts. The agreement among them was only 37% [8], leading to the discrepancies in diagnoses and indirectly

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resulting in the bias in epidemiological data of gastric cancer. Most pathologists in China follow the WHO diagnostic criteria, resemble to the Western diagnostic system [9]. Obviously, the findings of Japanese and South Korean studies on EGC are not applicable to Chinese patients. Therefore, we retrospectively analyzed 304 Chinese EGC cases to study the clinicopathological features under the WHO criteria, and to explore the risk factors of LNM in Chinese EGC patients in order to provide some useful suggestions for the standard treatment strategy of EGC in China.

2. Patients and methods

2.1. Study population

A total of 3016 patients with gastric cancer underwent radical gastrectomy or endoscopic resection at the Nantong First People's Hospital, Nantong, Jiangsu, China between 2002 and 2017, as well as the Haimen People's Hospital, Nantong, Jiangsu, China between 2014 and 2017 and at the Qidong People's Hospital, Nantong, Jiangsu, China between 2014 and 2017. Among them, 304 patients were diagnosed to have stage T1 gastric cancer (EGC) with complete clinicopathological data. We excluded remnant and metastatic cancers and none of these EGC patients had received radiotherapy or chemotherapy before surgery or endoscopic resection. 265 patients who underwent radical gastrectomy with D2 lymph node dissection and 39 patients who underwent ESD or EMR were involved in our study.

2.2. Patient's data

Patients' demographic data were gathered from the corresponding institutional database. The primary pathological slides were re-reviewed by three experienced pathologists to access the tumors' characteristics according to the *WHO Classification of Tumors of the Digestive System (2010)* [10]. The study was approved by the Ethics Committee of the Nantong First People's Hospital, the Haimen People's Hospital and the Qidong People's Hospital, respectively (201843, 2018001, 20180010). All specimens were handled and identified according to ethical and legal standards.

Clinicopathological features accessed included patients' gender, age, tumor location, tumor size, macroscopic type, histological type, differentiation degree, invasion depth, Lauren's type, tumor infiltration pattern (INF), ulceration, lymphoid follicles, lymphovascular invasion and perineural invasion.

The tumors were located at cardia, fundus, body, angle, antrum or pylorus. The maximum diameter was measured as the tumor size [11]. The macroscopic types were categorized as the following types: 0-I (protruded), 0-IIa (elevated), 0-IIb (flat), 0-IIc (depressed), and 0-III (excavated) [10].

The histological types include tubular adenocarcinoma (well differentiated and moderately differentiated), poorly differentiated adenocarcinoma, papillary adenocarcinoma, mucinous adenocarcinoma, and signet ring cell carcinoma. As for the differentiation degree, well and moderately differentiated tubular adenocarcinoma and papillary adenocarcinoma were classified as the differentiated type, and the poorly differentiated adenocarcinoma, signet-ring cell carcinoma and mucinous carcinoma as the undifferentiated type. The Lauren's type was established with intestinal type, diffuse type and mixed type.

The invasion depth was calculated based on the deepest point of the tumor penetration, and the lesions were then subdivided into 6 groups: M1 (confined to epithelium layer), M2 (intra-mucosa invasion without involvement of the muscularis mucosa), M3 (invasion of the muscularis mucosa), SM1 (invasion of the upper third of the submucosa), SM2 (invasion of the middle third of the submucosa), and SM3 (invasion of the lower third of the submucosa). Although there is no risk of lymph node metastasis in M1 lesions in theory, and the risk can also be ignored in fact, M1 cases were included in this study because this group of cases is a pre-invasive lesion and there is also possibility of lamina propria infiltration undetected. Endoscopists also conduct long-term endoscopic follow-up after ESD in M1 lesions.

For ESD/EMR cases, the depth of tumor invasion can only be determined and recorded when the vertical margin is negative for cancer invasion. When cancers invade the submucosa, we measure the distance (in μm) from the lower margin of the muscularis mucosa to the deepest part of the invading cancer. If the muscularis mucosae is obscure due to ulcerative changes, the depth should be measured on the virtual line based on the adjacent normal layer. If this measurement depth is <500 μm, we record it as SM1 (or T1b1), and if it is ≥ 500 μm, it is classified as SM2 (or T1b2) [5]. The above-mentioned vertical infiltration distance is measured by micrographics.

Tumor infiltrative patterns into the surrounding tissue (INF) included: INFa (expanding growth and a clear border with surrounding tissue), INFc (infiltrating growth and an unclear border with surrounding tissue, and INFb (between a and c) (Fig. 1) [12]. The diagnosis of intratumoral ulcerative was principally made based on the histological evidence of ulcerative findings [3,5].Histopathologically, an ulcer is defined as a mucosal defect which is deeper than the muscularis mucosae. An ulcer base with clear margins can be observed that penetrates the muscularis propria and into the submucosa. Inflammatory debris on the epithelial surface is often present. Fibrosis can be seen in the submucosa. However, a biopsy-derived scar should be excluded, which is usually a fibrosis restricted to small areas that can pass through

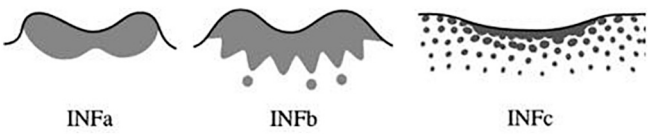

Fig. 1. Tumor infiltrative (INF) pattern (from reference [12]).

Table 1
Clinicopathologic features of 304 EGC patients.

Clinicopathologic features			Value (%)
Age	≤40		8(2.6)
	41–60		101(33.2)
	>60		195(64.1)
Gender	Male		202(66.4)
	Female		102(33.6)
Tumor location	Cardia, Fundus		33(10.9)
	Body		81(26.6)
	Angle		50(16.4)
	Antrum, pylorus		140(46.1)
Tumor size (cm)	≤2.0		198(65.1)
	>2.0		106(34.9)
Macroscopic type	0-I		47(15.5)
	0-II		119(39.1)
	0-III		138(45.4)
Histologic type	Tub1		34(11.2)
	Tub2, Pap		159(52.3)
	Por		73(24.0)
	Sig, Muc		38(12.5)
Lauren's type	Intestinal		177(58.2)
	Diffused		90(29.6)
	Mixed		37(12.2)
Invasion depth	T1a 156(51.3)	M1	4(1.3)
		M2	54(17.8)
		M3	98(32.2)
	T1b 148(48.7)	SM1	29(9.5)
		SM2	70(23.0)
		SM3	49(16.1)
Tumor infiltration pattern	a		94(30.9)
	b		78(25.7)
	c		132(43.4)

Tub1: well differentiated tubular adenocarcinoma. Tub2: moderately differentiated tubular adenocarcinoma. Por: poorly differentiated adenocarcinoma; Pap: papillary adenocarcinoma; Sig: signet ring cell carcinoma; Muc: mucinous adenocarcinoma.

Table 2
Univariate analysis predicting LNM in 265 EGC patients.

Clinicopathologic features	n	Lymph node metastasis, n		LNM (+)	Test value	P value
		Absence	Presence			
Gender					3.449	0.068
Male	176	149	27	15.3%		
Female	89	67	22	24.7%		
Age (years)					1.985	0.422
≤40	8	5	3	37.5%		
41–60	94	72	16	18.2%		
>60	169	139	30	17.2%		
Tumor location					6.216	0.100
Cardia, Fundus	26	24	2	7.7%		
Body	77	57	20	26.0%		
Angle	43	38	5	11.6%		
Antrum, Pylorus	119	97	22	18.5%		
Tumor size (cm)					2.167	0.146
≤2.0	165	139	26	15.8%		
>2.0	100	77	23	23.0%		
Macroscopic type					6.440	0.041
0-I	39	32	7	17.9%		
0-II	93	83	10	10.8%		
0-III	133	101	32	24.1%		
Differentiation degree					7.007	0.010
Differentiated type	163	141	22	13.5%		
Undifferentiated type	102	75	27	26.5%		
Histological type					18.202	0.001
Muc	3	2	1	33.3%		
Pap	11	7	4	36.4%		
Por	69	46	23	33.3%		
Sig	30	27	3	10.0%		
Tub	152	134	18	11.8%		
Lauren's type					4.153	0.134
Intestinal	148	127	21	14.2%		
Mixed	35	27	8	22.9%		
Diffused	82	62	20	24.4%		
Invasion depth					34.376	<0.001
M1	2	2	0	0.0%		
M2	40	40	0	0.0%		
M3	81	75	6	7.4%		
SM1	28	22	6	21.4%		
SM2	66	46	20	30.3%		
SM3	48	31	17	35.4%		
Infiltration pattern					19.930	<0.001
a	74	68	6	8.1%		
b	67	61	6	9.0%		
c	124	87	37	29.8%		
Lymphovascular invasion					51.350	<0.001
No	191	176	15	7.9%		
Yes	74	40	34	45.9%		
Lymphoid follicles					2.426	0.119
No	25	17	8	32.0%		
Yes	240	199	41	17.1%		
Ulceration					5.084	0.033
No	167	143	24	14.4%		
Yes	98	73	25	25.5%		
Perineural invasion					0.897	0.307
No	259	212	47	18.1%		
Yes	6	4	2	33.3%		

the muscularis mucosa sometimes.

2.3. Statistical analysis

Statistical analysis was performed by means of the SPSS 19.0 program. Univariate analysis was performed by means of Chi-square test or Fisher's exact test, and the Logistic regression was adopted to determine the independent risk factors. *P* Values<0.05 were considered statistically significant.

3. Results

3.1. Patient's characters

Among the 3016 gastric cancer patients, the 304 EGC patients accounted for 10.1% of the total. The clinicopathological features of the 304 patients were shown in Table 1. The median age of the patients was 64 years (31–88) and the median tumor size was 2.0 cm (0.3 cm–4.0 cm). Gender distribution was 202 males to 102 females. As for the tumor location, nearly half of the tumors were located at antrum or pylorus. The major macroscopic type in this study was 0-III. The percentage of well differentiated tubular adenocarcinoma was 11.2%, significantly lower than 24.8% (34/304 vs 2752/11104, $\chi^2 = 29.650$, $p < 0.001$) and 19.9% (34/304 vs 41/206, $\chi^2 = 7.442$, $p = 0.006$) reported by Japan

Table 3
Multivariate analysis predicting LNM in 265 EGC patients.

	Regression coefficient	Standard error	Wald $\chi 2$	P value	Odds ratio
Macroscopic type 0-I	1.102	0.706	2.434	0.119	3.009
Macroscopic type 0-III	0.464	0.491	0.891	0.345	1.590
Differentiated degree	−0.297	0.874	0.115	0.734	0.743
Histological type: muc	0.776	1.494	0.270	0.603	2.173
Histological type: pap	1.578	0.823	3.678	0.055	4.843
Histological type: por	0.938	0.851	1.214	0.270	2.554
Depth of invasion SM1	0.103	0.737	0.020	0.889	1.109
Depth of invasion SM2	0.808	0.594	1.852	0.174	2.244
Depth of invasion SM3	0.338	0.645	0.274	0.601	1.402
Infiltration pattern b	0.219	0.693	0.100	0.752	1.245
Infiltration pattern c	1.231	0.607	4.118	0.042	3.424
Lymphovascular invasion	1.879	0.424	19.687	<0.001	6.549
Ulceration	0.927	0.439	4.453	0.035	2.527

(well differentiated tubular adenocarcinoma/EGC) [2] and South Korean (well differentiated tubular adenocarcinoma/EGC) [13], but parallel to 11.9% (34/304 vs 8/67, $\chi^2 = 0.031$, $p = 0.860$) in a Western report (well differentiated tubular adenocarcinoma/EGC) [14].

156 T1a tumors occupied 51.3% of the whole group, including 4 tumors of M1, 54 tumors of M2 and 98 tumors of M3, and 148 T1b tumors accounted for 48.7%, including 29 tumors of SM1, 70 tumors of SM2 and 49 tumors of SM3. According to the Lauren's type, the majority of the cases were classified into intestinal type.

In 39 cases of gastric EMR/ESD in this study, 38 cases showed negative horizontal and vertical margins and no lymphovascular infiltration in histopathological assessment, which were considered to be curative. The 1 remaining case showed negative vertical margin and positive horizontal margin. One month later, gastrectomy was performed. Pathological examination showed iatrogenic ulcer, no residual cancer and no metastasis of lymph node. No recurrence or metastasis was found in all 39 cases during follow-up, of which 6 cases were lost after 1–2 times of follow-up.

3.2. Risk factors of lymph node metastasis in EGC

Among the 265 patients who had undergone radical gastrectomy with lymph node dissection, LNM existed in 49 patients (18.5%). As displayed in Table 2, univariate analysis showed that macroscopic type ($p = 0.041$), differentiation degree ($p = 0.010$), histological type ($p = 0.001$), invasion depth ($p < 0.001$), tumor infiltration pattern ($p < 0.001$), lymphovascular invasion ($p < 0.001$) and ulceration ($p = 0.033$) were correlated with LNM in EGC. As shown in Table 3, multivariate analysis revealed that lymphovascular invasion ($p < 0.001$, OR = 6.549), ulceration ($p = 0.035$, OR = 2.527) and INFc ($p = 0.042$, OR = 3.424) were the independent risk factors of LNM in EGC.

4. Discussion

In China, the detection rate of EGC is less than 10% [1]. In this present study, 304 EGC cases accounted for 10.1% of the total 3016 gastric cancers in the same period of this region, suggesting that the detection of EGC in this region was at the general level in China. In recent years, with rapid development of endoscopic technology, ESD offered equivalent results to surgical treatment. The data from Japan and Europe both showed that the 5-year survival rate of EGC patients after EMR/ESD exceeded 90%. Nevertheless, EMR and ESD must not be applied to tumors with LNM. LNM is regarded as a cause of recurrence

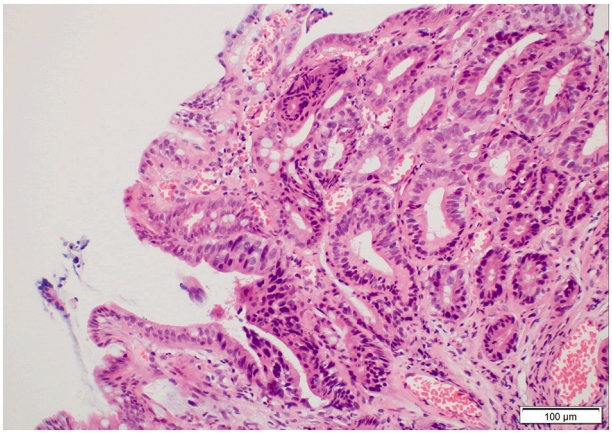

Fig. 2. The gastric mucosal biopsy was diagnosed as high grade intraepithelial neoplasia for no definite infiltration, while it may be diagnossed as well-differentiated adenocarcinoma based on the Japanese standard. (HE*200).

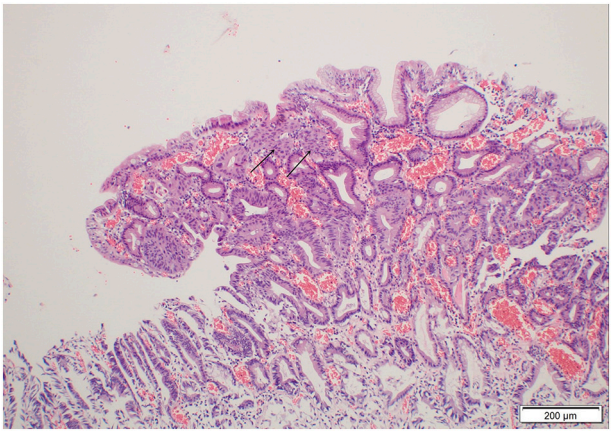

Fig. 3. Same case ESD slides showed that infiltrating cancer had invaded into the lamina propria. As shown by the arrow, the tumor glands infiltrate between the normal glands. (HE*100).

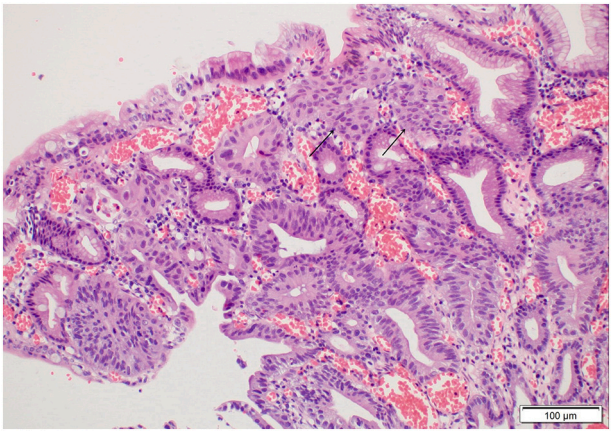

Fig. 4. Fig. 2 High field-amplified showed that infiltrating cancer had invaded into the lamina propria. As shown by the arrow, the tumor glands infiltrate between the normal glands. (HE*200).

and is the most important signal of poor prognosis. Patients with LNM need additional radical gastrectomy with lymph node dissection [5,8-10].

The diagnostic criteria of EGC in Japan are quite different from those of the WHO, which is a representative of the Western diagnostic system [8]. Most pathologists in China have adopted the WHO standards, which are stricter than those of Japanese. According to the Western standards, cancer can only be diagnosed when cancer infiltration is seen [15]. As shown in Fig. 2, due to no definite infiltration, the biopsy is diagnosed as high grade intraepithelial neoplasia, while the diagnosis is well- differentiated adenocarcinoma based on the Japanese standard. However, after ESD, as displayed in Figs. 3 and 4, tumor has invaded into the lamina propria. The results of our study also reflected the difference in diagnostic standards. In this study, the rate of well differentiated tubular adenocarcinoma is 11.2%, significantly lower than 24.8% [2] ($p < 0.001$), 19.9% [13] ($p = 0.006$) showed in Japanese and South Korean reports, but similar to 11.9% [14] ($p = 0.860$) showed in a Western report. The Chinese pathologists may be more cautious than their counterparts of Japanese and South Korean in diagnosis of well differentiated adenocarcinoma according to the Western standards that carcinoma can be diagnosed only when a single cell or small cell nest infiltrates the lamina propria, so the rate of well differentiated adenocarcinoma is obviously lower than those reported by Japanese and South Korean.

The rate of T1b invasion in our EGC cases (48.7%) was also higher compared to Japanese and South Korean data (43.4%–45.6% [13,16,17]), but lower than in Western data (53.8%–69.8% [14,18,19]), suggesting the relatively conservative attitude of Chinese and Western pathologists in the diagnosis of EGCs to some degree. Because of the difference in diagnostic criteria, the rates of early pT1-stage well-differentiated adenocarcinoma patients are lower in China than those in Japanese and Korean, and many conclusions of Japanese and Korean studies on EGC may not be suitable to Chinese patients. Based on the WHO histologic diagnosis standards, the Chinese pathologists usually apply more stringent histologic standards to diagnosis in EGC, so this difference should be taken into account when developing treatment strategies for EGC in China. Furthermore, Japanese and Korean conclusions on predictions of LNM risk should be thought over if applied to Chinese patients.

This study showed 18.5% (49/265) of LNM in EGC, a little bit higher than the percentage in other Chinese reports (12.3%–18.3%) [20-22], higher than that in Japanese and South Korean reports (9.4%–12.3%) [13,16,17,23], and lower than that in Western reports (22.4%–30.8%) [14,18,19]. This may reflect the differences of diagnostic criteria of EGC, which result in the increase in the number of cases of infiltrating submucosa, especially submucosa deep layer of EGC, leading to increased LNM rate of EGC patients. Indirectly. According to the Japanese guidelines for gastric cancer treatment 2014 (4th edition) [3], endoscopic resection is suitable for tumors in which the risk of LNM can be ignored and it must be en bloc resection. The accuracy of endoscopic ultrasonography (EUS) and computed tomography (CT) scans to predictive LNM is low. In a study of 1042 EGC patients, positive LNM patients predicted by CT accounted for only 12.2% of the actual positive patients, while positive LNM patients predicted by EUS accounted for only 9.1% of the actual positive patients [24]. Thus, the analysis of the clinicopathological characteristics of EGC is still more valuable for the prediction of LNM.

Univariate analysis showed that macroscopic type, differentiation degree, histological type, invasion depth, tumor infiltration pattern, lymphovascular invasion and ulceration were related to LNM in EGC, but gender, age, tumor location, Lauren's type, lymphoid follicles and perineural invasion were not statistically connected with LNM. Multivariate analysis demonstrated that lymphovascular invasion, ulceration and tumor infiltration pattern were independent risk factors for LNM, corresponding to many previous studies [13,14,23,26].

It has been reported that gender is an independent risk factor for LNM in EGC: the prevalence of EGCs is higher in males than in females, but the incidence of LNM is higher in females than in males [25,26]. In fact, this study exactly showed the similar difference, but the difference is not statistically significant. Age is also a risk factor for LNM in EGC reported in a previous literature: LNM is higher in patients under 40 years old than above 40 years old (33.3% vs 13%, $p < 0.01$) [27]. Our results (37.5% vs 17.2%, $p = 0.301$) are similar to theirs, but the statistical analysis showed no correlation between age and LNM, just like the results on gender. This may result from the small number of patients under the age of 40 (only 8) in this group, which may have an impact on the results of the statistical analysis.

Interestingly, there were different classifications on histological types to analyze LNM risk. In this work, WHO histological classification and Lauren's classification of gastric cancer were used. We showed that the histological type was the risk factor of LNM (univariate analysis), but not the independent risk factor (multivariate analysis). Some studies suggested that Lauren's classification was an independent risk factor for LNM [20,27], but this study wss not able to verify this point.

According to the WHO classification, Fang C et al. classified EGCs into six types: tubular, papillary, poorly cohesive, micropapillary, pancreatic acinar-like types and others and found that poorly cohesive carcinoma was an independent risk factor of LNM [9], while Chen L et al. subtyped EGCs into another six types: tubular, papillary, poorly cohesive, mucinous, micropapillary adenocarcinoma and mixed adenocarcinoma with signet-ring cell carcinoma, and concluded that mixed adenocarcinoma with signet-ring cell carcinoma was an independent factor of LNM [21]. Gastric cancer is a highly heterogeneous disease. There was an inevitable subjectivity in the determination of histological classifications in various research reports, especially in the inconsistent definition of mixed type, which may be the reason of unmatched conclusions. The histological manifestation of tumor is the result of interaction between molecular abnormality and tumor microenvironment. The study of histology characteristics related to biological behavior of gastric cancer, especially the accurate definition of mixed adenocarcinoma, might provide important information for LNM risk assessment of gastric cancer.

The results of this study indicate that China and Western countries have obvious differences from Japan and South Korea in pathological diagnosis criteria of early well-differentiated adenocarcinoma, which may influence the treatment strategy of EGC. Lymphovascular invasion and ulceration are independent risk factors for LNM in EGC. Thus, for evaluation of LNM risk and prognosis of EGC, detailed pathological examination of EMR/ESD specimens is essential, especially to recognize the intralymphovascular embolus.

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