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ORIGINAL ARTICLE

Risk Factors for Lymph Node Metastasis in Early Gastric Cancer with Signet Ring Cell Carcinoma

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Abstract
Background Gastrectomy was reported to be an excessive approach for early gastric cancer with signet ring cell carcinoma. This study was conducted to explore the feasibility of endoscopic submucosal dissection for early gastric with signet ring cell carcinoma.
Methods Data from 1067 patients who underwent gastrectomy for early gastric cancer were collected retrospectively. The association between the clinicopathological factors and the lymph node metastasis was analyzed by univariate and multivariate logistic regression analyses.
Results Lymph node metastasis was confirmed in 17.2 % (184/1067) of patients. Meanwhile, the incidence of lymph node metastasis with each histology type was 13.1 % (26/198), 9.8 % (34/347), and 23.8 % (124/522) for signet ring cell carcinoma, differentiated carcinomas, and undifferentiated carcinomas, respectively. Signet ring cell carcinoma occurs more in women and young patients, with a higher predominance for mucosa. Various factors—including sex, tumor size, depth of tumor, and lymphovascular invasion—were found to be associated with lymph node metastasis for signet ring cell carcinoma ($P<0.05$). Multivariate analysis revealed that tumor size (7.489, 95 % CI 2.025–27.701) and lymphovascular invasion (18.434, 95 % CI 3.256–104.359) were independent risk factors for lymph node metastasis ($P<0.05$). Further analysis reveals there was no positive lymph node in patients with signet ring cell carcinoma when tumor confined to mucosa, size ≤2 cm and without lymphovascular invasion and ulceration.
Conclusions Given the low risk of lymph node involvement, we recommend that endoscopic submucosal dissection be safely applied for early gastric signet ring cell carcinoma when tumor confined to mucosa, size ≤2 cm, and without lymphovascular invasion and ulceration.

Keywords Gastric cancer · Signet ring cell carcinoma · Lymph node metastasis · Endoscopic submucosal dissection

Abbreviations

DCs	differentiated carcinomas
EGC	early gastric cancer
ESD	endoscopic submucosal dissection
LNM	lymph node metastasis
LVI	lymphovascular invasion
LNM	lymph node metastasis
SRC	signet ring cell carcinoma
UDCs	undifferentiated carcinomas

Introduction

The prognosis for patients with early gastric cancer (EGC) after gastrectomy is excellent. The 5-year survival is more than 90 %

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as confirmed in both Japanese and Western studies.[1] Though the gastrectomy with lymphadenectomy is the standard treatment for EGC, the lymph node dissection may be an excessively aggressive procedure for EGC because of the low risk of lymph node metastasis (LNM). Endoscopic resection is an alternative to radical gastrectomy in EGC of well or moderately differentiated tubular adenocarcinoma when tumor size ≤2 cm, free of ulcer, and confined to the mucosa.[2] The application of endoscopy treatment obtained the equivalent long-term outcomes and better quality of life compared to surgery.[3]

The criteria of endoscopy treatment are too strict that a considerable number of EGC patients without LNM still received gastrectomy. As the development of endoscopic submucosal dissection (ESD), the lesion size was no longer the limitation for the endoscopic resection. Recently, some authors proposed expanded indications for the endoscopic treatment.[4,5] According to Japanese gastric cancer treatment guidelines, ESD for undifferentiated type tumors clinically diagnosed as T1a and less than 2 cm in diameter without lymphovascular invasion and ulceration is regarded as an investigational treatment (expanded indication).[6] Regarding the incidence of lymph node metastasis, the expanded indication of ESD is still in debate.[7–9]

Undifferentiated carcinomas (UDCs) included poorly differentiated carcinoma, mucinous carcinoma, and signet ring cell carcinoma (SRC). Earlier studies reported that SRC has favorable biological features.[10] It is worthy to note that most studies primarily focused on comparison of SRC and non-SRC types, few investigate the difference between SRC and other UDCs.[11] As the histopathologic type was an important factor for the choice of endoscopy treatment, the purpose of the present study was primarily to compare the characteristics of SRC with other UDC types, especially the rate of lymph node metastasis. In this study, we retrospectively investigated the risk factors of nodal metastases in a large cohort of 1067 EGC patients to propose a practical therapeutic strategy for early gastric SRC.

Materials and Methods

We retrospectively reviewed 1067 patients with histologically proven early gastric cancer, who underwent curative gastrectomy with lymph node dissection, at the Department of Abdominal Surgery, Cancer Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, Beijing, China, from January 2002 to December 2013. Remnant gastric cancer, chemotherapy before surgery, and those combined with advanced gastric cancer were excluded. This study received institutional review board approval.

All patients underwent a gastrectomy with D2 lymph node dissection. Early gastric cancer is defined as a lesion confined to the mucosa or the submucosa (T1), regardless of the presence of lymph node metastases.[12] According to invasion depth, T1 lesion is divided into T1a (tumor invades lamina propria or muscularis mucosae) and T1b (tumor invades submucosa). The macroscopic appearance of early gastric cancer was analyzed in accordance with the Japanese Classification of Gastric Cancer[12] specified therein: elevated type, I and IIa; flat type, IIb; or depressed type, IIc and III. The diagnosis of lymph node metastases, depth of invasion, and histologic type were determined by qualified pathologists. Pathologic diagnosis and classifications were made on the basis of the World Health Organization and Japanese Classification of Gastric Carcinoma.[12] The tumors are histologically classified into differentiated carcinomas (DCs) and undifferentiated carcinomas. The former includes papillary adenocarcinoma and well and moderately differentiated tubular adenocarcinoma, whereas the latter includes poorly differentiated adenocarcinoma, signet ring cell carcinoma, and mucinous adenocarcinoma. Lymph node metastasis and depth of tumor invasion were classified according to the 7th edition of the American Joint Committee on Cancer/International Union Against Cancer (AJCC/UICC) TNM staging system.[13] SRC was defined as >50 % of the tumor consisting of isolated or small groups of malignant, cells containing intracytoplasmic mucin, according to the World Health Organization classification. A single sample of all dissected lymph nodes obtained by a cross-section through the hilus at the central portion was examined. Lymphovascular invasion (LVI) was defined as presence of tumor emboli either in lymphatic duct or vascular lumen. Lesions with ulceration or scarring from previous ulceration (converging folds or deformity of the muscularis propria, or fibrosis in the submucosal or deeper layer) within them were regarded as ulcerated lesions.[14]

Clinicopathological characteristics, such as sex, age, tumor location, size, macroscopic type, depth of tumor, lymph node retrieved, lymph node metastasis, LVI, and ulceration, were compared between SRC group, DC group, and other UDCs group, respectively. Univariate and multivariate analyses were performed to investigate the risk factors of lymph node metastasis for SRC and other UDCs. Then, the odds ratio risk of lymph node metastasis was calculated between cancers with different histologic types.

Follow-up of the entire study population was conducted until death or the cutoff date (December 31, 2014), by means of regular outpatient clinic consultation or communication with patients through telephone and letter. Median and mean follow-up period were 48 and 53.6 months (range, 0.36–156.96), respectively.

Statistical Analysis

Descriptive data are presented as the mean±SD. For between group comparisons, continuous variables were analyzed using the Student's *t* test and categorical variables with the chi-square test. Factors found to be significant ($P<0.05$) in univariate analysis were included in subsequent multivariate

logistic regression analysis in order to identify independent variables associated with lymph node metastases. All statistical analyses were undertaken using the Statistical Package for the Social Sciences (SPSS) for Windows, Version 17.0 (SPSS Inc., Chicago, IL, USA). A probability value of less than 0.05 was considered significant.

Results

Clinicopathological Characteristics

Among the 1067 patients, the mean age was 55.3±11.5 years old (20–83 years) with a male to female ratio of 2.01:1. The average tumor size was 2.62±1.59 cm (0.1–10.6). One hundred eighty-four (17.2 %) patients exhibited lymph node metastasis. The incidence of lymph node metastasis for tumor confined to submucosa (25.8 %, 134/519) was obviously higher than mucosa (9.1 %, 50/548). The percentage of patients with each histopathologic type was 32.5 % (347/1067) with DCs, 48.4 % (516/1067) with poorly differentiated carcinoma, 0.6 % (6/1067) with mucinous carcinoma, and 18.6 % (198/1067) with SRC, respectively.

Comparison According to Histological Classification

We compared the patients with SRC histology with those with UDCs and DCs, respectively. Among the histological types, SRC type has a higher prevalence in females (49.5 %, 98/198) and younger patients (49.9±11.5) and a higher predominance

Table 1 Clinicopathological characteristics of EGC patients according to histological classification

Variables	SRC	DCs		UDCs	
	n (%)	*n* (%)	*P*	*n* (%)	*P*
EGC (total, *n*=1067)	198 (18.6 %)	347 (32.5 %)		522 (48.9 %)	
Age (year)	49.9±11.5	59.6±10.2	0.000*	54.5±11.4	0.000*
Sex					
Male	100 (50.5)	265 (76.4)	0.000*	347 (66.5)	0.000*
Female	98 (49.5)	82 (23.6)		175 (33.5)	
Location					
Upper third	2 (1.0)	54 (15.6)	0.000*	33 (6.3)	0.010*
Middle third	25 (12.6)	50 (14.4)		72 (13.8)	
Lower third	171 (86.4)	243 (70.0)		417 (79.9)	
Tumor size (cm)	2.64±1.55	2.52±1.58	0.407	2.67±1.62	0.778
Macroscopic					
Elevated	24 (12.1)	67 (19.3)	0.071	77 (14.8)	0.046*
Flat	55 (27.8)	79 (22.8)		101 (19.3)	
Depressed	119 (60.1)	201 (57.9)		344 (65.9)	
Tumor depth					
T1a	141 (71.2)	164 (47.3)	0.000*	243 (46.6)	0.000*
T1b	57 (28.8)	183 (52.7)		279 (53.4)	
Lymph node retrieved	20.3±10.8	19.2±11.3	0.246	22.3±12.8	0.045*
LNM					
Negative	172 (86.9)	313 (90.2)	0.232	398 (76.2)	0.002*
Positive	26 (13.1)	34 (9.8)		124 (23.8)	
LVI					
No	188 (94.9)	321 (92.5)	0.270	469 (89.8)	0.030*
Yes	10 (5.1)	26 (7.5)		53 (10.2)	
Ulceration					
No	183 (92.4)	325 (93.7)	0.581	479 (91.8)	0.771
Yes	15 (7.6)	22 (6.3)		43 (8.2)	

Characteristics of SRC histology type are compared with DCs and UDCs, respectively

EGC early gastric cancer, *DCs* differentiated cancers, *UDCs* undifferentiated carcinomas, *SRC* signet ring cell carcinoma, *LNM* lymph node metastasis, *LVI* lymphovascular invasion

*$P<0.05$

for mucosa (71.2 %, 141/198) compared to other histologic types. Compared with DCs and UDCs, SRC (99.0 %, 196 of 198) mainly located in the middle and distal part of stomach. There was no difference between groups in tumor size and ulceration. Macroscopic type, lymph node retrieved, lymph node metastasis, and LVI differed significantly between SRC and UDCs ($P<0.05$), whereas there was no difference between SRC and DCs ($P>0.05$) (Table 1).

Univariate and Multivariate Analyses for Lymph Node Metastasis Risk

In order to observe the LNM risk factors of SRC and UDCs, univariate and multivariate analyses were performed. In univariate analysis, sex, tumor size, tumor depth, and LVI were all found associated with LNM for SRC and UDCs. Multivariate analysis revealed that tumor size (7.489, 95 % CI 2.025–27.701) and LVI (18.434, 95 % CI 3.256–104.359) were correlated with LNM in SRC, while sex (1.741, 95 % CI 1.113–2.722), depth of tumor (2.403, 95 % CI 1.490–3.874), and LVI (4.854, 95 % CI 2.560–9.207) were with UDCs (Tables 2 and 3).

Further subgroup analysis of the tumor size reveals there was no difference in LNM between SRC and DCs (1.035, 95 % CI 0.253–4.239, $P>0.05$) when tumor ≤2 cm in diameter, whereas the risk of LNM of UDCs versus SRC is 7.147 (95 % CI 2.167–23.568, $P<0.05$) (Table 4). LNM was found in three early gastric SRC cases with size ≤20 mm. Clinicopathological variables of the three cases showed that ulceration, T1b, and LVI existed, respectively (Tables 5 and 6).

Survival Analysis

Univariate analysis revealed that old age, deeper invasion, lymph node metastasis, LVI, and differentiated type were significantly correlated with poor prognosis ($P<0.05$). Age

Table 2 Univariate and multivariate analyses of LNM risk factors for EGC with SRC

Variable	LNM in SRC (*n*, %)		*P*	Odds ratio (95 % CI)	*P*
	−	+			
Age					
≤55 years	116 (67.4)	22 (84.6)	0.076		
>55 years	56 (32.6)	4 (15.4)			
Sex					
Male	92 (53.5)	8 (30.8)	0.031*		
Female	80 (46.5)	18 (69.2)		2.662 (0.985–7.196)	0.054
Location					
Upper third	2 (1.2)	0 (0.0)	0.511		
Middle third	23 (13.4)	2 (7.7)			
Lower third	147 (85.5)	24 (92.3)			
Tumor size					
≤2 cm	88 (51.2)	3 (11.5)	0.000*		
>2 cm	84 (48.8)	23 (88.5)		7.489 (2.025–27.701)	0.003*
Macroscopic					
Elevated	22 (12.8)	2 (7.7)	0.592		
Flat	46 (26.7)	9 (34.6)			
Depressed	104 (60.5)	15 (57.7)			
Tumor depth					
T1a	127 (73.8)	14 (53.8)	0.036*		
T1b	45 (26.2)	12 (46.2)		1.076 (0.373–3.106)	0.892
LVI					
No	169 (98.3)	19 (73.1)	0.000*		
Yes	3 (1.7)	7 (26.9)		18.434 (3.256–104.359)	0.001*
Ulceration					
No	159 (92.4)	24 (92.3)	1.000		
Yes	13 (7.6)	2 (7.7)			

EGC early gastric cancer, *SRC* signet ring cell carcinoma, *LNM* lymph node metastasis, lymphovascular invasion
*$P<0.05$

Table 3 Univariate and multivariate analyses of LNM risk factors for EGC with UDCs

Variable	LNM in UDCs (*n*, %)				
	−	+	*P*	Odds ratio (95 % CI)	*P*
Age					
≤55 years	209 (52.5)	62 (50.0)	0.625		
>55 years	189 (47.5)	62 (50.0)			
Sex					
Male	277 (69.6)	70 (56.5)	0.007*		
Female	121 (30.4)	54 (43.5)		1.741 (1.113–2.722)	0.015*
Location					
Upper third	29 (7.3)	4 (3.2)	0.267		
Middle third	54 (13.6)	18 (14.5)			
Lower third	315 (79.1)	102 (82.3)			
Tumor size					
≤2 cm	197 (49.5)	48 (38.7)	0.036*		
>2 cm	201 (50.5)	76 (61.3)		1.345 (0.866–2.090)	0.187
Macroscopic					
Elevated	54 (13.6)	23 (18.5)	0.338		
Flat	76 (19.1)	25 (20.2)			
Depressed	268 (67.3)	76 (61.3)			
Tumor depth					
T1a	211 (53.0)	32 (25.8)	0.000*		
T1b	187 (47.0)	92 (74.2)		2.403 (1.490–3.874)	0.000*
LVI					
No	379 (95.2)	90 (72.6)	0.000*		
Yes	19 (4.8)	34 (27.4)		4.854 (2.560–9.207)	0.000*
Ulceration					
No	364 (91.5)	115 (92.7)	0.650		
Yes	34 (8.5)	9 (7.3)			

EGC early gastric cancer, *UDCs* undifferentiated carcinomas, *LNM* lymph node metastasis, *LVI* lymphovascular invasion

*$P<0.05$

(4.307, 95 % CI 2.305–8.049), LNM (2.392, 95 % CI 1.350–4.237), and LVI (2.264, 95 % CI 1.162–4.409) are independent prognostic factors for EGC in multivariate analysis ($P<0.05$). The 5-year and 10-year overall survival in patients without LNM was 95 and 85 %, respectively. Meanwhile, it was 85 and 76 % for patients with LNM (log-rank, $P=0.001$) (Table 7).

Discussion

Patients with early gastric carcinoma generally have a good prognosis after adequate surgical resection, as shown by a 5-year survival rate of more than 90 % worldwide. Though debate existed for decades regarding the appropriate extent of lymphadenectomy for gastric adenocarcinoma, nowadays,

Table 4 Multivariate analysis of lymph node metastasis between histopathological types in the subgroup of tumor size

	Tumor ≤2 cm		Tumor >2 cm	
	Odds ratio (95 % CI)	P	Odds ratio (95 % CI)	*P*
Histopathological type				
Signet ring cell carcinoma	1		1	
Differentiated carcinomas	1.035 (0.253–4.239)	0.962	0.715 (0.387–1.321)	0.284
Undifferentiated carcinomas	7.147 (2.167–23.568)	0.001*	1.381 (0.812–2.349)	0.234

*$P<0.05$

Table 5 Classification of early gastric SRC according to depth, tumor size, and LVI

		Mucosa (*n*, %)			Submucosa (*n*, %)		
		≤20 mm	20–30 mm	>30 mm	≤20 mm	20–30 mm	>30 mm
LVI	No	1/70 (1.4)	5/40 (12.5)	7/30 (23.3)	1/19 (5.3)	3/18 (16.7)	2/11 (18.2)
	Yes	0/0 (0.0)	0/0 (0.0)	1/1 (100.0)	1/2 (50.0)	3/3 (100.0)	2/4 (50.0)

SRC signet ring cell carcinoma, *LVI* lymphovascular invasion

both Eastern and Western approaches are favoring D2 lymphadenectomy as a standard procedure.[15] However, as a matter of excellent prognosis of early gastric cancer, the application of gastrectomy and lymph node dissection may be too excessive.

The gastrectomy may be associated with long-term disorders including reflux esophagitis, gastritis of the remnant stomach, dumping syndrome, anemia, osteoporosis, and cancer of the remnant stomach. It has been widely accepted that endoscopic submucosal dissection (ESD) has less morbidity and mortality than gastrectomy in the treatment of EGC and comparable survival in a long-term prognosis.[3] Consequently, ESD was recommended as an alternate treatment for EGC by Japanese gastric cancer treatment guidelines. Due to the higher rate of LNM in the undifferentiated histologic type, the accepted indications for endoscopic resection has been limited to EGC of differentiated carcinoma without ulcerative findings, of which the depth of invasion is clinically diagnosed as T1a and ≤2 cm.[6] These indications were established because of the technical limitations of endoscopic mucosal resection.[16] The criteria of endoscopic resection treatment are so strict that a considerable number of EGC patients with negative lymph node received gastrectomy. A few of stratification methods to identify patients who have negligible risk for developing lymph node metastasis were studied to optimize the selection of patients who can be cured by endoscopic resection.[17]

According to Japanese gastric cancer treatment guidelines, ESD for undifferentiated type tumors clinically diagnosed as T1a and less than 2 cm in diameter without LVI and ulceration is regarded as an investigational treatment (expanded indication).[6] As there is amount of conflicting results, whether or not expanding the indication of ESD is still in debate.[7–9] Poorly differentiated carcinoma, mucinous carcinoma, and signet ring cell carcinoma are grouped as undifferentiated carcinoma. Many studies have reported that SRC has more favorable clinicopathological characteristics than other UDC cell types, but there are still uncertainties with regard to the role of ESD for SRC.[18]

Ha et al.[19] reported that SRC had no LNM in the case of a mucosal tumor, smaller than 2 cm, and in the absence of lymphatic involvement. Lee et al.[20] drew a similar conclusion. They found that the rate of lymph node metastasis was similar for both signet ring cell and differentiated type (10.7 versus 9.0 %, respectively; $P=0.307$), but the LNM occurred in 13 % SRC with size <2 cm. Consequently, they suggested EGC with SRC should be treated by gastrectomy with lymph node dissection. In the light of these considerations, the aim of the present study was to clarify the biologic behavior of the early SRCs by comparing the clinicopathological features and the incidence of lymph node metastasis of SRC with other histologic types and to propose the suitable procedure for SRC.

The proportion of SRC in EGC was 18.6 % (198/1067), which is consistent with previous studies.[11,21] Our study showed that SRC has younger age (49.9±11.5, $P<0.05$), more female (49.5 %, 98/198), more locate in the lower third of stomach (86.4 %, 171/198), and dominant in the mucosa (71.2 %, 141/198). SRC has comparative lymph node metastasis rate and LVI with DCs ($P>0.05$), whereas SRC differed significantly from those of UDCs (13.1 versus 23.8 % and 5.1 versus 10.2 %, respectively; $P<0.05$). Though Cox multivariate analysis showed age, LNM, and LVI were independent prognostic factors for EGC ($P<0.05$), the histology type did not affect the long-term survival. These results suggested SRC has a unique biologic nature and more favorable features than other UDC types as reported.[22] Most SRC was found confined to mucosa in this study. Lehnert et al.[23] reported that although the entire mucosa showed a rich supply of blood capillaries, lymph capillaries were distributed only in the deep gastric lamina propria adjacent to and within the muscularis mucosae, whereas submucosa has abundant lymph ducts. In our study, the lower LNM risk may attribute to the features that SRC

Table 6 Clinicopathological variables of three early gastric SRC patients with tumor size ≤2 cm

Case	Age	Sex	Location	Size	Macroscopic type	T	LVI	LNM	Ulceration
1	36	F	Lower third	0.7	Flat	T1a	−	1/29	Yes
2	41	M	Lower third	0.8	Depressed	T1b	−	2/5	No
3	38	F	Lower third	1.5	Flat	T1b	+	1/20	No

SRC signet ring cell carcinoma, *LNM* lymph node metastasis, *LVI* lymphovascular invasion

Table 7 Univariate and multivariate analyses of prognostic factors for survival in early gastric cancer patients

Variables	Univariate analysis	Multivariate analysis	
	P value	Risk ratio (95 % CI)	*P* value
Age (≤55 vs. >55 years)	0.000*	4.307 (2.305–8.049)	0.000*
Gender (M vs. F)	0.137		
Tumor location (U vs. M vs. L)	0.054		
Tumor size (≤2 cm vs. >2 cm)	0.428		
Macroscopic type (elevated vs. flat vs. depressed)	0.285		
Depth of tumor (T1a vs. T1b)	0.048*	1.130 (0.664–1.925)	0.652
LNM (negative vs. positive)	0.001*	2.392 (1.350–4.237)	0.003*
LVI (absent vs. present)	0.000*	2.264 (1.162–4.409)	0.016*
Ulceration (no vs. yes)	0.277		
Histopathological type	0.000*		
(SRC vs. DCs)		2.405 (0.976–5.924)	0.056
(SRC vs. UDCs)		1.187 (0.474–2.973)	0.714

SRC signet ring cell carcinoma, *UDCs* undifferentiated carcinomas, *LNM* lymph node metastasis, *LVI* lymphovascular invasion

*$P<0.05$

type is prone to spread on the superficial surface, not invade deeply. Moreover, the SRC cells are easily spotted in biopsy specimens because of their typical enriched intracytoplasmic mucin and peripheral compressed nuclei. Consequently, SRC gastric carcinoma can be detected at an early stage. These reasons are factors to explain why SRC tumors behave relatively less aggressively in EGC.

The incidence of lymph node metastasis was the important basis for the EGC treatment. The risk factors for LNM need to be clarified before the decision. Except for LVI, multivariate analysis showed the LNM risk factors differed in SRC and UDCs. Tumor size (7.489, 95 % CI 2.025–27.701) and LVI (18.434, 95 % CI 3.256–104.359) were independent risk factors for SRC, whereas sex (1.741, 95 % CI 1.113–2.722), depth of invasion (2.403, 95 % CI 1.490–3.874), and LVI (4.854, 95 % CI 2.560–9.207) were for UDCs. This study confirmed female sex as an independent risk factor for UDCs. There have been conflicting reports on the effect of sex hormones on the development of gastric cancer. According to a meta-analysis, a longer period of fertility and hormonal replacement therapy were each associated with decreased gastric cancer risk. Longer exposure to the estrogen effects of either ovarian or exogenous origin was thought to decrease the risk of gastric cancer.[24] On the other hand, in an immunohistology study of 107 gastric cancer patients, the estrogen receptor-positive rate was slightly higher in younger female patients and in patients with poorly differentiated gastric cancer, and the 10-year survival rate after surgery was significantly lower in the estrogen receptor-positive cases.[25] The relationship between sex hormones and cancer development needs further investigation. Large tumors are frequently accompanied by other risk factors for lymph node metastasis, which is confirmed in this study. There was lower LNM risk for early gastric SRC with size ≤2 cm in diameter. Thus, it allowed the application of ESD for the smaller EGC with SRC histology.

Although ulceration is considered an important predictor for LNM in EGC,[26] our study did not reveal the relationship between the incidence of LNM and ulceration. But, ulceration factor was found in one out of three cases with LNM (Table 6). It implied that we could apply ESD to SRC with caution if we stick to the strict criteria. A recent study reported that ESD for undifferentiated EGC fulfilling the expanded criteria was achieved in 99.9 % (102/103) of en bloc and curative resection and yielded good long-term outcomes.[27] Regarding the relatively small sample in single center, we acknowledge that there could be a selection bias in our study. The conflicting outcomes from various papers suggested that a larger scale study is needed for more detailed analysis.

Based on the findings of our study, poorly differentiated and signet ring cell EGCs were shown to possess different clinicopathological features, especially the LNM risk. It implied that poorly differentiated EGC is more complicated than early SRC when considering endoscopic treatment. Thus, the expanded indication of endoscopic surgery for undifferentiated cancers should be interpreted with caution. Meanwhile, this study showed the biology nature of SRC was similar with those for DCs, but significantly different from those for other UDCs. Consequently, different treatment should be taken to apply to early UDCs according to the histologic type. Before the consensus of expanded indication for ESD, it is more reasonable to restrict the expanded indication for undifferentiated type to signet ring cell carcinoma. Herein, we suggested a practical guideline to follow for ESD. That is, endoscopic

submucosal resection can be safely employed for EGC with SRC when tumor confined to mucosa, no more than 2 cm, and without LVI and ulceration.

Conclusions

The significantly different outcomes between UDCs and SRC indicated that poorly differentiated EGC has a more aggressive nature than SRC, especially LNM. The low risk of lymph node involvement in early gastric SRC suggested that ESD could be applied for early gastric signet ring cell carcinoma when tumor confined to mucosa, size ≤2 cm, and without lymphovascular invasion and ulceration.

Competing Interests The authors declare that they have no competing interests.

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