



Retrospective Study

Risk of lymph node metastasis in mixed-type early gastric cancer determined by the extent of the poorly differentiated component

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Abstract

AIM: To predict the rate of lymph node (LN) metastasis in diffuse- and mixed-type early gastric cancers (EGC) for guidelines of the treatment.

METHODS: We reviewed 550 cases of EGC with

diffuse- and mixed-type histology. We investigated the clinicopathological factors and histopathological components that influence the probability of LN metastasis, including sex, age, site, gross type, presence of ulceration, tumour size, depth of invasion, perineural invasion, lymphovascular invasion, and LN metastasis status. We reviewed all slides and estimated the proportions of each tumour component; pure diffuse type, mixed-predominantly diffuse type (diffuse > intestinal type), mixed-predominantly intestinal type (intestinal > diffuse type), and mixed diffuse = intestinal type. We calculated the extents of the respective components.

RESULTS: LN metastasis was observed in 12.9% (71/550) of early gastric cancers cases [15/288 mucosal EGCs (5.2%) and 56/262 submucosal EGCs (21.4%)]. Of 550 cases, 302 were diffuse-type and 248 were mixed-type EGCs. Of 248 mixed-type EGCs, 163 were mixed-predominantly diffuse type, 82 were mixed-predominantly intestinal type, and 3 were mixed diffuse = intestinal type. Mixed-type cases with predominantly diffuse type histology showed a higher frequency of LN metastasis (20.2%) than cases of pure diffuse type (9.3%) and predominantly intestinal type (12.2%) histology. We measured the dimensions of each component (intestinal and diffuse type) to determine the association of the extent of each component with LN metastasis in mixed-type gastric carcinoma. The total tumour size and the extent of poorly differentiated components was associated with LN metastasis, while that of signet ring cell components was not.

CONCLUSION: We recommend careful identification and quantitative evaluation of mixed-type early gastric cancer components after endoscopic resection to determine the intensity of the treatment.

Key words: Lymph nodes; Metastasis; Gastric cancer; Histology; Endoscopic gastrointestinal surgery

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Core tip: This study consolidates correlations between clinicopathological characteristics of early gastric cancer and the risk of lymph node (LN) metastasis, which is important to select patients that will benefit from endoscopic submucosal dissection. This paper also shows that the amount of poorly differentiated tumor cells within mixed type early gastric cancer is correlated with the highest risk of LN metastasis, thus highlighting the need for diligent histological characterization of patient specimens.

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INTRODUCTION

Endoscopic submucosal dissection (ESD), a recently developed technique, is a widely accepted treatment modality for early gastric cancer (EGC), including for diffuse (undifferentiated) type EGC within the expanded criteria (mucosal cancer measuring less than 2 cm without ulceration and lymphovascular tumour emboli). Large datasets indicate almost no risk of lymph node (LN) metastasis in diffuse type EGCs^[1-3]. A considerable proportion of gastric adenocarcinomas show a mixed composition with both intestinal and diffuse histological components. No consensus has been established regarding the management of mixed-type histology, *i.e.*, varying proportions of diffuse and intestinal components in the tumour.

Generally, gastric adenocarcinoma can be subclassified into intestinal (differentiated) and diffuse (undifferentiated) types based on gland formation^[4,5]. According to Japanese guidelines, diffuse components are further subdivided into signet ring cell carcinoma and poorly differentiated carcinoma^[6]. These guidelines refer to mixed-type EGCs by their predominant histological component, whether intestinal or diffuse. There are several reports on the management and outcomes of mixed-type EGCs^[7-11]. Takizawa *et al*^[7] reported that mixed-predominantly diffuse type showed significant LN metastasis and suggested that their treatment be similar to that of diffuse-type EGCs. Hanaoka *et al*^[8] reported that the predominantly undifferentiated mixed-type tumours showed considerably higher LN metastasis than other types of submucosal invasive EGCs. Furthermore, Min *et al*^[9] reported that mixed intestinal- and diffuse-type EGCs could be managed with ESD under the expanded criteria.

We investigated 550 cases of diffuse- and mixed-type EGCs to determine which components of the diffuse subtypes (signet ring cell or poorly differentiated carcinoma) are more closely associated with LN metastasis, providing evidence to establish a consensus for the management of diffuse- and mixed-type EGCs with ESD.

MATERIALS AND METHODS

Patient selection and clinicopathological evaluation

We retrieved early gastric cancer cases that involved gastrectomies with LN dissection at the Pusan National University Hospital treated between 2008 and 2013, and selected 550 cases of EGC with diffuse- and mixed-type histology based on the Japanese classification of gastric cancer^[6]. Cases involving

Table 1 Clinicopathological factors and lymph node metastasis in early gastric cancers *n* (%)

	Total	Lymph node status		<i>P</i> value
		Negative (<i>n</i> = 479)	Positive (<i>n</i> = 71)	
Sex				0.950
Male	304	265 (87.2)	39 (12.8)	
Female	246	214 (87.0)	32 (13.0)	
Age (yr)	550	54.5 ± 0.7	55.5 ± 2.5	0.686
Site ¹				0.059
Upper	129	120 (93.0)	9 (7.0)	
Middle	252	217 (86.1)	35 (13.9)	
Lower	169	142 (84.0)	27 (16.0)	
Gross type				0.030
Elevated	59	45 (76.3)	14 (23.7)	
Flat	51	46 (90.2)	6 (9.8)	
Depressed	440	388 (88.2)	52 (11.8)	
Ulceration				0.640
Absent	445	389 (87.4)	56 (12.6)	
Present	105	90 (85.7)	15 (14.3)	
Tumour size (cm) ²				< 0.0001
≤ 1	40	39 (97.5)	1 (2.5)	
≤ 2	126	120 (95.2)	6 (4.8)	
≤ 3	141	125 (88.7)	16 (11.3)	
≤ 3	243	195 (80.2)	48 (19.8)	
Depth of invasion ³				< 0.0001
Mucosa	288	273 (94.8)	15 (5.2)	
M2	50	49 (98.0)	1 (2.0)	
M3	238	224 (94.1)	14 (5.9)	
Submucosa	262	206 (78.6)	56 (21.4)	
SM1	33	30 (90.9)	3 (9.1)	
SM2	67	55 (82.1)	12 (17.9)	
SM3	162	121 (74.7)	41 (25.3)	
Depth (µm)	262	1754 ± 89.4	2017 ± 130.3	0.153
Perineural invasion				< 0.0001
Absent	495	442 (89.3)	53 (10.7)	
Present	55	37 (67.3)	18 (32.7)	
LV invasion				< 0.0001
Absent	518	464 (89.6)	54 (10.4)	
Present	32	15 (46.9)	17 (53.1)	

¹Between upper *vs* middle+lower; ²Between ≤ 2 cm *vs* > 2 cm; ³Between M *vs* SM. LV: Lymphovascular; M2: Lamina propria invasion; M3: Muscularis mucosae invasion without penetration; SM1: Upper third; SM2: Middle third; SM3: Lower third.

preoperative chemotherapy or radiotherapy or multiple gastric cancers were excluded. Pathological reports and electronic medical records were reviewed, for attributes, including sex, age, site, gross type, presence of ulceration, tumour size, depth of invasion, perineural invasion, lymphovascular invasion, and LN metastasis status. Lesions were classified into the following three groups according to gross type: elevated type (I, IIa, IIa + IIb, and IIa + IIc), flat type (IIb, IIb + IIa, and IIb + IIc), and depressed type (IIc, IIc + IIb, IIc + III, IIc + IIa, and III). Ulceration was defined as a deformity of the muscularis propria or fibrosis in the submucosal layer. Intramucosal carcinoma was categorized as M2 (lamina propria invasion) or M3 (muscularis mucosae invasion without penetration). Submucosal invasion was graded as SM1 (upper third), SM2 (middle third), or SM3 (lower third). The depth of submucosal invasion was

measured directly using a micrometre and was defined as the distance from the lowest point of the muscularis mucosa (or surface of ulceration) to the point of deepest tumour penetration. The Institutional Review Board at the Hospital approved this study.

Histopathologic evaluation with regard to histological subtypes

We reviewed all slides and estimated the proportions of each tumour component. Diffuse components (undifferentiated) were further subdivided into signet ring cell (sig) or poorly differentiated (por) types. Subclassification was according to the most prevalent component, applying the 50% criterion, as follows: pure diffuse type, mixed-predominantly diffuse type (diffuse > intestinal type), mixed-predominantly intestinal type (intestinal type > diffuse), and mixed diffuse = intestinal type^[7]. We calculated the extents of the respective components using the following formula: extent of respective component (cm) = dimension of tumour (cm) × estimated percentage of the respective component/100.

Statistical analysis

Statistical calculations were performed using SPSS for Windows (version 12K, Chicago, IL, United States). To identify the predictive risk factors for LN metastasis, the data were statistically analysed using the chi-squared test and an unpaired Student's *t* test. The independent factors for LN metastasis in diffuse- and mixed-type EGCs were analysed by binary logistic regression analysis (backward, stepwise). The ability of histological component extent to predict LN metastasis was assessed using receiver operating characteristic (ROC) curve analysis. The total areas under the ROC curves ranged from 0.5 to 1.0, with 1.0 indicating perfect predictive value and 0.5 indicating random chance. A pairwise comparison of the areas under the ROC curve was subsequently performed to assess the predictive value of each histological component. A *P* < 0.05 was deemed statistically significant.

RESULTS

Clinicopathological characteristics relevant to LN metastasis

Clinicopathological characteristics as a status of LN metastasis are listed in Table 1. Of 550 cases, 71 (12.9%) showed LN metastasis [15/288 mucosal EGCs (5.2%) and 56/262 submucosal EGCs (21.4%)]. Increased tumour size, gross type (elevated), depth of invasion, and perineural and lymphovascular invasion were associated with LN metastasis. Furthermore, we investigated the independent predictive risk factors for LN metastasis using binary logistic regression analysis (Supplemental Table 1). Tumour size (*P* = 0.001), depth of invasion (*P* < 0.0001), and lymphovascular invasion (*P* = 0.001) were independent predictive risk

Table 2 Lymph node metastasis according to depth of invasion, ulceration, and tumour size *n* (%)

	Mucosal carcinoma				Submucosal carcinoma			
	No ulcer		Ulcer		SM1		SM2	SM3
	≤ 2 cm	> 2 cm	≤ 3 cm	> 3 cm	≤ 3 cm	> 3 cm	Any size	
Diffuse (<i>n</i> = 302)	1/61 (1.6)	5/86 (5.8)	2/22 (9.0)	1/19 (5.3)	0/12 (0)	2/7 (28.6)	6/32 (18.8)	11/63 (17.5)
Mixed (<i>n</i> = 248)	0/19 (0)	5/64 (7.8)	0/4 (0)	1/10 (10)	0/6 (0)	1/8 (12.5)	6/35 (17.1)	30/99 (30.3)
Total (<i>n</i> = 550)	1/80 (1.3)	10/150 (6.7)	2/26 (7.7)	2/29 (6.9)	0/18 (0)	3/15 (20.0)	12/67 (17.9)	41/162 (25.3)

SM1: Upper third; SM2: Middle third; SM3: Lower third.

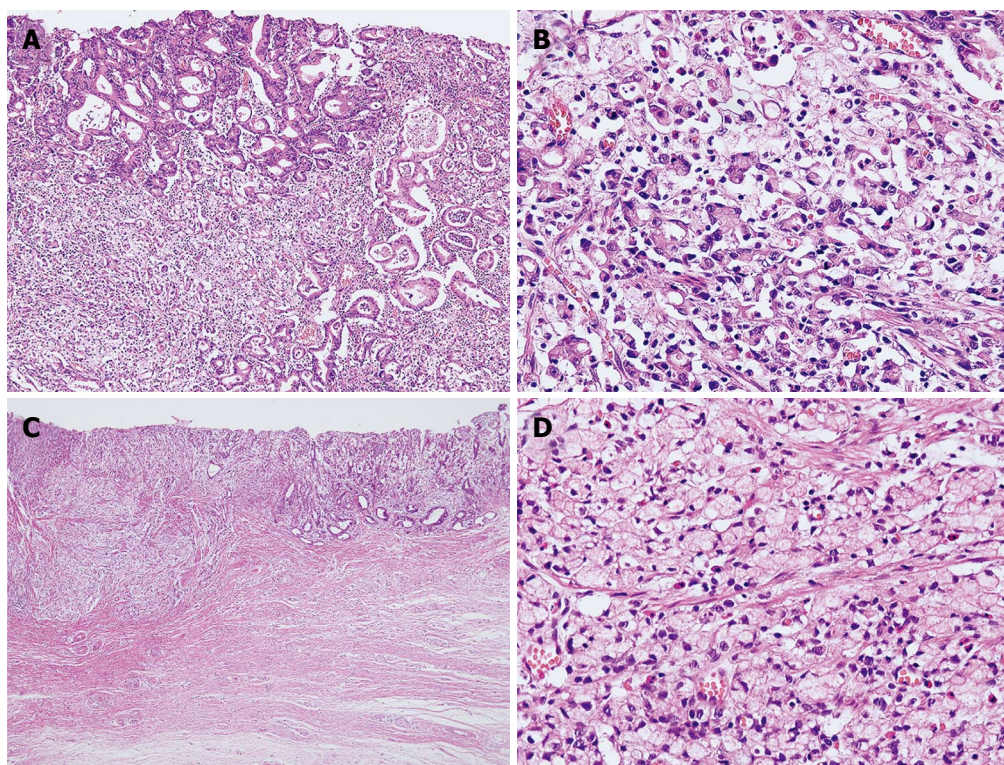


Figure 1 Pathology of mixed-type gastric carcinoma. A: Mixed-type gastric carcinoma showing moderately differentiated tubular adenocarcinoma, intestinal type (upper left and right) and poorly differentiated adenocarcinoma (lower left); B: High magnification view of poorly differentiated lesion ($\times 400$); C: Mixed-type gastric carcinoma showing moderately differentiated tubular adenocarcinoma, intestinal type (right) and signet ring cell carcinoma (left); D: High magnification view of signet ring cell carcinoma lesion ($\times 400$).

factors for LN metastasis in diffuse- and mixed-type EGCs. In our dataset, there were 80 cases of mucosal EGCs less than 2.0 cm in size and without ulceration; among them, only 1 case showed LN metastasis (Table 2). Hence, only 1 case within ESD eligibility criteria showed LN metastasis in this study.

Histological subtypes and LN metastasis

Of 550 cases, 302 were diffuse-type and 248 were mixed-type EGCs (Figure 1; Supplemental Tables 2 and 3). Furthermore, 28 of the 302 diffuse-type (9.3%) and 43 of the 248 mixed-type EGCs (21.0%) showed LN metastasis. The clinicopathological features associated with LN metastasis in each type were similar to those associated with LN metastasis when diffuse and mixed types were considered together, e.g., tumour size, depth of invasion, and perineural and lymphovascular tumour invasion. Depth of

submucosal invasion was significantly associated with LN metastasis in mixed-type ($P = 0.044$), but not in diffuse-type EGCs ($P = 0.905$)

Of 248 mixed-type EGCs, 163 were mixed-predominantly diffuse type, 82 were mixed-predominantly intestinal type, and 3 were mixed diffuse = intestinal type (Table 3). Interestingly, LN metastasis was more frequent in the mixed-predominantly diffuse type (33/163, 20.2%) than in either the pure diffuse type (28/302, 9.3%) or the mixed-predominantly intestinal histological type (10/82, 12.2%; $P = 0.003$).

Quantitative impact of histopathological subtypes on LN metastasis

We measured the extent of the individual components to determine the quantitative power of each to predict LN metastasis. The total tumour size and the

Table 3 Histopathological subtypes and lymph node metastasis *n* (%)

	Total	Status of lymph node metastasis	
		Negative	Positive
Pure diffuse type	302	274 (90.7)	28 (9.3) ^a
Sig	233	210 (90.1)	23 (9.9)
Por	69	64 (92.8)	5 (7.2)
Mixed type	248	205 (83.7)	43 (16.3)
Predominantly diffuse	163	130 (79.8)	33 (20.2) ^a
Sig predominant	107	86 (80.4)	21 (19.6)
Por predominant	56	44 (78.6)	12 (21.4)
Predominantly intestinal	82	72 (87.8)	10 (12.2) ^a
Diffuse = intestinal	3	3 (100.0)	0 (0.0)

^a*P* = 0.003 (between pure diffuse, predominantly diffuse, and predominantly intestinal). Sig: Signet ring cell; Por: Poorly differentiated.

Table 4 Relationship between the extent of various histopathological components and lymph node metastasis in 550 diffuse- and mixed-type early gastric cancers

	Lymph node status		<i>P</i> value
	Negative (<i>n</i> = 479)	Positive (<i>n</i> = 71)	
Total (cm)	3.30 ± 0.09	4.46 ± 0.29	< 0.001
Diffuse type (cm)	2.73 ± 0.11	3.61 ± 0.24	0.005
Signet ring cell	2.07 ± 0.12	2.54 ± 0.29	0.161
Poorly differentiated	0.66 ± 0.05	1.07 ± 0.20	0.012
Intestinal type (cm)	0.65 ± 0.05	0.87 ± 0.17	0.172

extent of the poorly differentiated component were significantly larger in the metastatic LN group (Table 4). Interestingly, the extent of the poorly differentiated component was associated with LN metastasis (*P* = 0.012), whereas that of the signet ring cell component was not (*P* = 0.161).

In the 248 mixed-type EGCs, we assessed the ability of the histological components to predict LN metastasis using ROC curve analysis (Figure 2). The areas under the ROC curve for each component were as follows: diffuse component (0.687, 95%CI: 0.604-0.701, *P* < 0.0001), total size (0.610, 95%CI: 0.523-0.698, *P* = 0.023), poorly differentiated component (0.598, 95%CI: 0.505-0.691, *P* = 0.043), and signet ring cell component (0.556, 95%CI: 0.450-0.661, *P* = 0.249). These results confirm that poorly differentiated component was significantly associated with LN metastasis (*P* = 0.043) while signet ring cell component was not (*P* = 0.249).

DISCUSSION

With the development of ESD, the criteria for diffuse-type EGCs eligible for endoscopic resection expanded to include mucosal lesions measuring less than 2.0 cm without ulceration or lymphovascular tumour emboli; this was based on the risk of LN metastasis^[1-3]. Hirasawa *et al.*^[12] reported that 310 diffuse-type EGCs within the expanded criteria showed no LN metastasis,

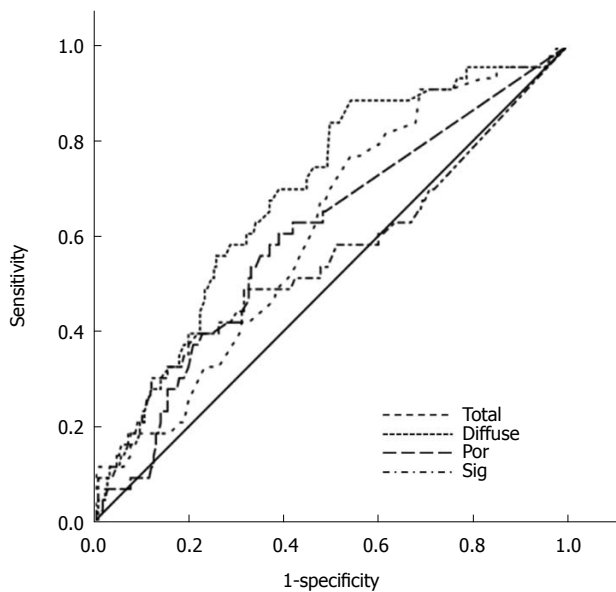


Figure 2 Receiver operating characteristics curve analysis of scores for predicting lymph node metastasis in mixed-type early gastric cancers yielded an area under the curve of 0.687 (95%CI: 0.604-0.701, *P* < 0.0001) for the diffuse component, 0.610 (95%CI: 0.523-0.698, *P* = 0.023) for total size, 0.598 (95%CI: 0.505-0.691, *P* = 0.043) for the poorly differentiated component, and 0.556 (95%CI: 0.450-0.661, *P* = 0.249) for the signet ring cell component.

in contrast to an earlier report by Gotoda *et al.*^[13]. Shim and Lee summarized previously published datasets describing the risks of LN metastasis for diffuse-type EGCs that meet the proposed criteria^[3], concluding that these expanded criteria for ESD of diffuse type EGC are feasible with regard to efficacy and safety.

Consistent with other reports that reported low or no LN metastasis rates, we noted only one such metastasis among cases within the established expanded ESD criteria (1/80, 1.3%). We also identified various clinicopathological factors associated with LN metastasis, including increased size, gross type (elevated), depth of invasion, and perineural and lymphovascular invasion; this was consistent with previously published data^[14,15]. Taken together, the expanded criteria for diffuse-type EGC can be used to determine the primary option for treatment. Mixed- predominantly diffuse EGCs showed a higher frequency of LN metastasis (20.2%) than either the pure diffuse type (9.3%) or the mixed-predominantly intestinal type (12.2%), in accordance with previous reports^[7,8], suggesting that mixed-predominantly diffuse EGC should be more stringently managed than pure diffuse-type EGC.

We further sub-categorized diffuse histological components into signet ring cell and poorly differentiated carcinoma, and evaluated the impact of each component on LN metastasis. Interestingly, we identified an increase in the extent of the total diffuse component - especially the poorly differentiated

component - was associated with LN metastasis. There was no such association between the extents of signet ring cell components or intestinal components with LN metastasis. Furthermore, ROC curve analysis of mixed-type EGCs showed that the total tumour size along with the extents of the diffuse and poorly differentiated components affected LN metastasis with statistical significance, while the extent of the signet ring cell component did not (Figure 2).

Many studies reported favourable outcomes of early signet ring cell carcinoma and recommended endoscopic resection as the primary treatment option, which is not the case for poorly differentiated carcinoma^[16-18]. Ha *et al*^[17] demonstrated that signet ring cell carcinoma within the expanded criteria showed no LN metastasis and favourable outcomes compared to undifferentiated carcinoma. Kim *et al*^[18] reported that signet ring cell carcinoma had a lower rate of LN metastasis compared to poorly differentiated or tubular adenocarcinoma of the submucosal type. However, none of aforementioned studies demonstrated the association of signet ring cell carcinoma in mixed-type EGCs with LN metastasis. This study demonstrates that a larger, poorly differentiated histological component was associated with LN metastasis, whereas a larger signet ring cell component was not.

There are many limitations and possible errors in our method of measuring the exact size of the lesions. We measured the extent of each component by multiplying the percentage of each component with the largest diameter of the lesion. Although this method is not perfect, we believed that it would be sufficiently indicative of the role of each component.

In conclusion, our results support the use of the extended criteria for the therapeutic use of ESD in cases of diffuse-type EGCs, and we recommend careful identification and quantitative evaluation of each tumour component in mixed-type EGC specimens obtained by endoscopic resection.

ACKNOWLEDGMENTS

This study was presented in part at the 2015 USCAP meeting (Boston, MA, United States).

COMMENTS

Background

A considerable proportion of gastric adenocarcinomas show a mixed composition with both intestinal and diffuse histological components. No consensus has been established regarding the management of mixed-type histology.

Research frontiers

The authors investigated which components of the diffuse subtypes (signet ring cell or poorly differentiated carcinoma) are more closely associated with lymph node (LN) metastasis, providing evidence to establish a consensus for the management of diffuse- and mixed-type early gastric cancers (EGCs) with endoscopic submucosal dissection (ESD).

Innovations and breakthrough

This study consolidates correlations between clinicopathological characteristics of early gastric cancer and the risk of LN metastasis, which is important to select patients that will benefit from endoscopic submucosal dissection. This paper also shows that the amount of poorly differentiated tumor cells within mixed type early gastric cancer is correlated with the highest risk of LN metastasis.

Applications

The results of our present study support the use of the extended criteria for the therapeutic use of ESD in cases of diffuse-type EGCs, recommending careful identification and quantitative evaluation of each tumour component in mixed-type EGC specimens obtained by endoscopic resection.

Terminology

Gastric adenocarcinoma can be subclassified into intestinal (differentiated) and diffuse (undifferentiated) types based on gland formation. Diffuse components are further subdivided into signet ring cell carcinoma and poorly differentiated carcinoma. In practice, mixed-type EGCs, consisted of intestinal and diffuse type, are frequently encountered. The expanded criteria for ESD include diffuse (undifferentiated) mucosal EGC measuring less than 2 cm without ulceration and lymphovascular tumour emboli.

Peer-review

This paper shows that the amount of poorly differentiated tumor cells within mixed type early gastric cancer is correlated with the risk of LN metastasis. They emphasize the need for diligent histological characterization of patient specimens as conclusion. Their findings are interesting and useful for the future treatment of early gastric cancer.

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