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The comparison of clinicopathological characteristics of two distinct manifestations of gastric signet ring cell carcinoma under EUS

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ABSTRACT

Background and Objectives: There are two different endoscopic ultrasonographic manifestations of gastric signet ring cell carcinoma (GSRCC). No studies have been reported on the differences in the clinical profiles of patients based on EUS examination. We aim to study the variations in clinicopathological characteristics between two distinct endoscopic ultrasonographic manifestations of GSRCC.

Methods: A total of 302 patients with GSRCC confirmed by pathological examination who underwent EUS were enrolled in the study. Based on the endoscopic ultrasonographic features, patients were categorized into two groups: type 1, where the entire layer structure disappeared, and type 2, where the layer structure was still present and appeared lymphomatoid. Clinicopathologic features were collected retrospectively and analyzed.

Results: Compared with type 2 patients, type 1 patients tended to develop GSRCC at an older age ($P = 0.033$) and had higher serum levels of tumor markers and were more likely to experience anemia ($P < 0.001$) and weight loss ($P < 0.001$) during the disease progression. Significant increases in the tumor size ($P < 0.001$), thickness of the affected gastric wall ($P < 0.001$), and depth of tumor invasion ($P < 0.001$) were observed in type 1 patients. Furthermore, type 1 patients had higher prevalence of affected blood vessels ($P < 0.001$), nerves ($P < 0.001$), lymph nodes ($P < 0.001$), and peritoneal metastasis ($P < 0.001$). However, no difference was found in the duration of disease between the two groups, and all deficient mismatch repairs were observed in type 1 patients.

Conclusions: The two distinct endoscopic ultrasonographic manifestations of GSRCC exhibited different clinicopathological characteristics, suggesting that they may represent different subtypes of the disease that require special attention in management strategies.

Key words: EUS; Gastric cancer; Gastric signet ring cell carcinoma; Lymphoma; Clinicopathologic feature

INTRODUCTION

Gastric signet ring cell carcinoma (GSRCC) is a highly malignant carcinoma mucocellulare[1] characterized by the presence of more than 50% of tumor cells with large mucin vacuoles filling the cytoplasm.[2] Unlike the decline incidence of gastric cancer, studies have revealed a persistent rise in the incidence of GSRCC,[3] accounting for 35% to 45% of newly diagnosed cases of gastric adenocarcinoma.[4,5] Significant progress has been made in understanding the epidemiology, pathology, and molecular mechanisms of GSRCC, which has facilitated its clinical management.[6] However, due to the unique biological characteristics of GSRCC, with some tumors extending only to the intramucosal layer without vertical invasion reaching diameters of more than 10 cm, whereas others tend to invade the submucosal layer even at the early stage,[7] the accuracy of preoperative staging and diagnosis of GSRCC remains a great challenge in clinical practice.

EUS enables the differentiation of the anatomic structural layers of the gastric wall and reveals remarkable differences in their echogenic appearance when a tumor has invaded. EUS is considered to be the most valuable tool for tumor T staging.[8,9] However, the accuracy of EUS for T staging varies considerably, ranging from 64.8% to 92%.[10,11] GSRCC had a significantly higher risk of understaging that warrants attention.[9] Under EUS, GSRCC exhibits two distinct ultrasonographic features: one is the complete disappearance of the entire layer structure; the other is that the layer structure of the gastric wall was still present with the mucosal muscle layer, submucosa, and muscularis propria mainly diffuse thickening, which is similar to the changes of lymphoma.[9,12]

However, there is a lack of data regarding potential differences in the clinical characteristics of these two distinct endoscopic manifestations. The aim of the present study was to compare the clinicopathological characteristics of individuals with GSRCC based on the distinct EUS manifestations.

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METHODS

Patient selection

Using "signet ring cell carcinoma" as a keyword, the medical record system of Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, was searched to collect patients diagnosed with GSRCC in the pathological results who underwent EUS from January 1, 2020, to December 31, 2023. All patients included in this analysis met the following criteria: (1) their disease was pathologically confirmed as GSRCC; (2) they underwent preoperative stage using EUS. The exclusion criteria were as follows: (1) outpatient with incomplete clinical profile; (2) operation that was preceded by preoperative chemoradiotherapy; (3) patients with synchronous malignancies or previous other primary cancers; and (4) tumors with bulky obstruction or alterations in gastrointestinal anatomical that EUS failed to pass through. The study was approved by the ethics committee of Tongji Medical College, Huazhong University of Science and Technology (no. IORG0003571). All patients signed informed consent for EUS operation, and data had been anonymized and deidentified.

EUS procedures

Curved heteroscope with a 360-degree radial echoendoscope (Olympus processor EU-ME2; Olympus, Tokyo, Japan) was used. Three hundred milliliters to 800 mL of de-aerated water or fitted with a water-filled balloon were utilized to assist acoustic coupling and to improve transmission of the ultrasound beam. Analogous to pathologic classification, the extent of wall invasion was imaged as a hypoechoic disruption and evaluated based on the tumor infiltration into each layer.[13] Assessment of tumor invasion depth by EUS and all patients were staged using the eighth edition of the AJCC TNM staging system.[14] All operations were performed by an experienced gastroenterologist with a track record of more than 1000 EUSs per year.

According to the differences of endoscopic ultrasonographic manifestations, patients were categorized into two types: type 1, consisting of patients with endoscopic ultrasonographic manifestation with the disappearance and incrassation of the entire layers of the gastric wall; and type 2, consisting of patients similar to gastric lymphoma, characterized by the intact gastric wall hierarchical structure, primarily incrassation of the mucosal muscle layer, submucosa, or muscularis propria [Figure 1].

Data collection

The clinicopathological profiles including the medical history, examination results, and treatment selections of the patients enrolled in the present study were collected and reviewed retrospectively [Figure 2].

Statistically analysis

Measurement data are presented as mean ± standard deviation or median and quartile (25%–75% percentile), whereas count data are presented as frequency and percentage. The independent-sample t test was used to compare groups that met the assumptions of normality and homogeneity of variance. Conversely, the nonparametric rank-sum test was used to compare groups that did not meet the criteria of normality and homogeneity of variance. The (corrected) χ^2 test or Fisher exact probability method was used to analyze unordered count data, whereas the nonparametric rank-sum test was used to analyze single-group ordered rank data. Statistical analysis was conducted using IBM SPSS Statistics

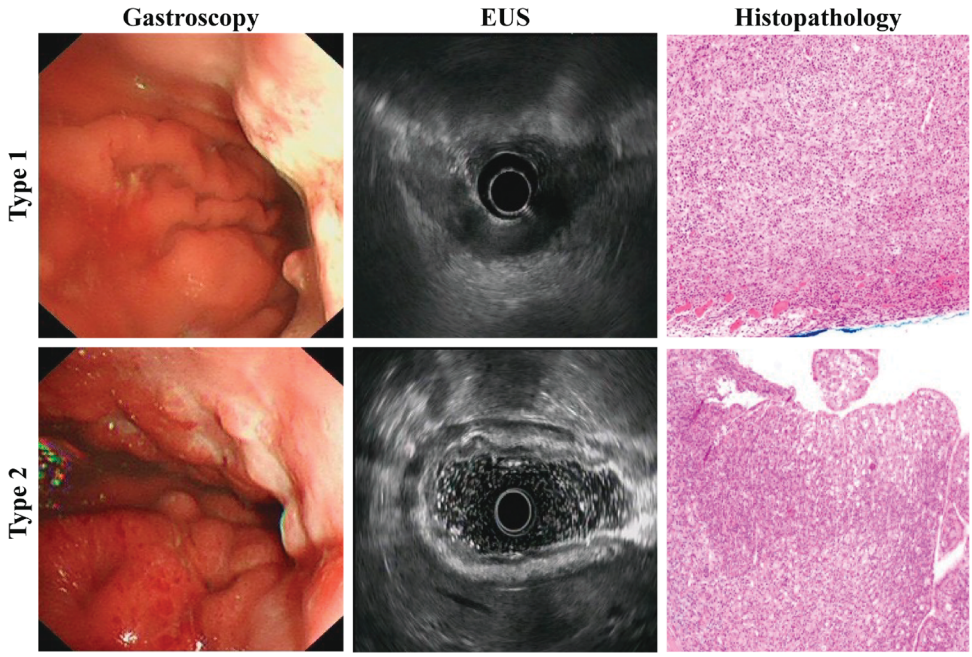

Figure 1. EUS manifestation criteria for classifying patients. Type 1: disappearance and incrassation of the entire layers of the gastric wall under EUS. Type 2: intact gastric wall hierarchical structure, primarily incrassation of the mucosal muscle layer, submucosa, or muscularis propria similar to gastric lymphoma under EUS.

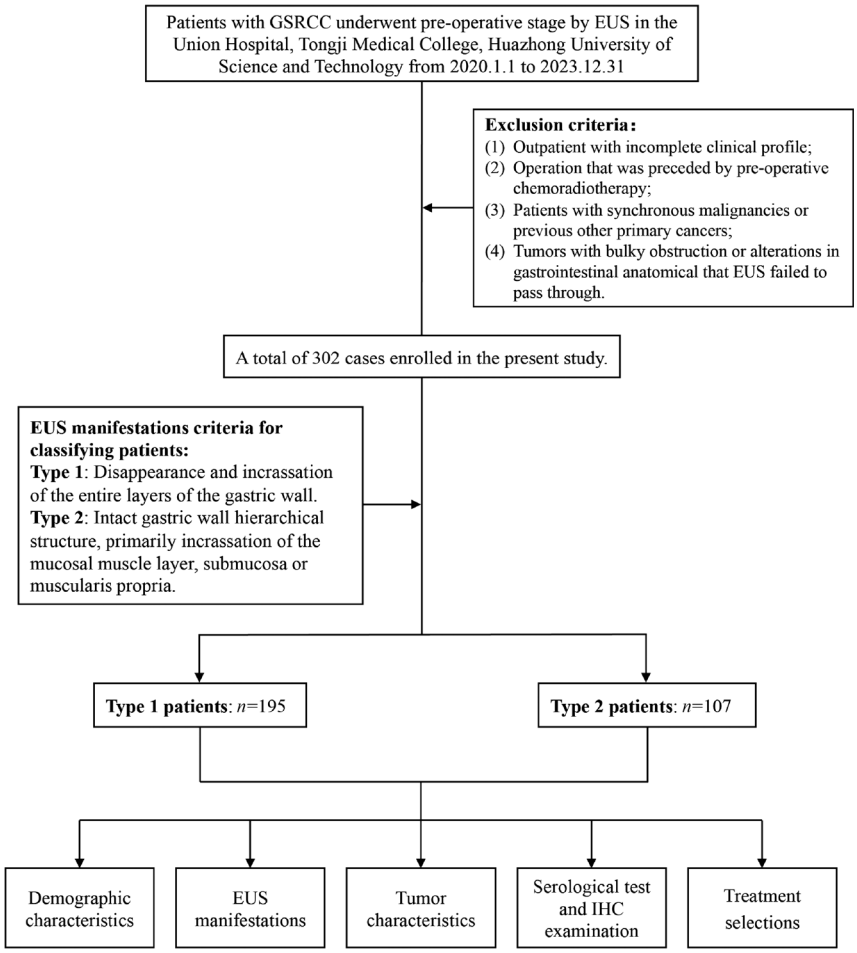

Figure 2. Flow diagram demonstrating study design. GSRCC: Gastric signet ring cell carcinoma; IHC: Immunohistochemical.

software (version 26.0; IBM Corp, Armonk, NY). Significance was determined based on a threshold of $P \leq 0.05$ for all models.

RESULTS

Demographic characteristics

A total of 302 cases were included in the present study, comprising 195 cases of type 1 and 107 cases of type 2. Significant differences in age and gender were observed in the present study. Specifically, individuals of type 1 were found to be of older age compared with those of type 2 ($P = 0.033$). Additionally, males had a higher frequency of developing GSRCC of type 1 ($P = 0.017$). The study also revealed a notable disparity in weight reduction, wherein more type 1 patients experienced weight loss throughout the course of disease (47.18% vs 21.50%, $P < 0.001$). Further details are presented in Table 1.

EUS manifestations

GSRCC commonly developed lesions in multiple sites of the stomach, with the gastric body, sinus pylorus, gastric angle, and pylorus being the most frequently affected areas. The findings presented in Table 2 indicate that type 1 GSRCC were more frequently observed in the gastric fundus ($P = 0.042$) and gastric angle ($P = 0.002$). Furthermore, significant increases in the tumor size and thickness of the affected gastric wall ($P < 0.001$), as well as increased depth of tumor invasion ($P < 0.001$), were observed in type 1 patients.

Tumor characteristics

The components of tumors were compared additionally between type 1 and type 2 patients, but no significant difference was found [Table 3]. However, a higher proportion of type 1 patients showed affected blood vessel, nerve, and lymph node ($P < 0.001$). Regarding lymph node metastasis sites, it was observed that more type 1 patients developed lymph node metastasis in sites adjacent to gastric lesser curvature ($P = 0.001$), gastric greater curvature ($P = 0.005$), hepatogastric space ($P < 0.001$), and retroperitoneum ($P = 0.008$). A higher proportion of type 2 patients presented at early T and N stages, accompanied by a lower incidence of distant metastasis. Additionally, individuals of type 1 exhibited a higher prevalence of peritoneal metastasis (16.41% *vs* 2.80%, $P < 0.001$).

Serological test and immunohistochemical examination results

The current results revealed that more patients of type 1 exhibited elevated serum levels of carcinoembryonic antigen ($P = 0.006$), carbohydrate antigen 125 (CA-125, $P = 0.048$), carbohydrate antigen 19.9 (CA-19.9, $P = 0.036$), and carbohydrate antigen 7.24

Table 1

The demographic characteristics of enrolled patients

	Type 1 (*n* = 195)	Type 2 (*n* = 107)	*P* value
Age, y			0.033
<55	65 (33.33)	49 (45.79)	
≥55	130 (66.67)	58 (54.21)	
Gender			0.017
Male	119 (61.03)	50 (46.73)	
Female	76 (38.97)	57 (53.27)	
Menopausal status			0.400
Premenopause	24 (31.58)	22 (38.60)	
Postmenopause	52 (68.42)	35 (61.40)	
Body mass index	22.56 ± 3.97	22.35 ± 2.95	0.628
Past history			
Cardiovascular disease	10 (5.13)	1 (0.93)	0.063
Hypertension	38 (19.49)	21 (19.63)	0.977
Diabetes	10 (5.13)	5 (4.67)	0.862
Cerebrovascular disease	3 (1.54)	3 (2.80)	0.451
Helicobacter pylori infection	24 (12.31)	11 (10.28)	0.599
Family history of gastrointestinal malignant tumors	12 (6.15)	6 (5.61)	0.848
Personal history			
Smoking	45 (23.08)	21 (19.63)	0.488
Alcohol consumption	33 (16.92)	12 (11.21)	0.183
Present history			
Course of disease in months	2.00 (1.00, 6.00)	2.50 (0.50, 12.00)	0.908
Abdominal pain	130 (66.67)	68 (63.55)	0.586
Abdominal distension	52 (26.67)	20 (18.69)	0.120
Gastrointestinal hemorrhage	31 (15.90)	17 (15.89)	0.998
Weight reduction	92 (47.18)	23 (21.50)	<0.001
Weight reduction, kg	4.00 (2.13, 5.00)	4.00 (2.00, 5.00)	0.686
Acid reflux, nausea, or emesis	79 (40.51)	36 (33.64)	0.240
Onset of symptoms were associated with eating	33 (16.92)	19 (17.76)	0.854
Before or after eating			0.760
Before eating	10 (30.30)	5 (26.32)	
After eating	23 (69.70)	14 (73.68)	

(CA-7.24, $P = 0.014$) and more likely to develop anemia ($P < 0.001$; Table 4). No significant difference was observed in the expression of phosphoenolpyruvate carboxykinase ($P = 0.361$) and human epidermal growth factor receptor 2 ($P = 0.233$) between the two types of patients in the immunohistochemical examination. Furthermore, a total of 84 patients received immunohistochemical examination

Table 2

The endoscopic ultrasonographic manifestations of enrolled patients

	Type 1 (*n* = 195)	Type 2 (*n* = 107)	*P* value
Tumor location			
Cardia	41 (21.03)	13 (12.15)	0.054
Gastric fundus	28 (14.36)	7 (6.54)	0.042
Gastric body	93 (47.69)	55 (51.4)	0.537
Gastric angle	82 (42.05)	26 (24.3)	0.002
Sinus pylorus	91 (46.67)	38 (35.51)	0.061
Ulcers combination	161 (82.56)	81 (75.7)	0.153
Diseased gastric wall thickness, mm	14.80 (11.60, 18.70)	7.70 (5.13, 11.38)	<0.001
Maximum diameter of tumor size, cm	4.00 (3.00, 7.00)	2.00 (1.30, 3.15)	<0.001
Depth of tumor invasion			<0.001
Lamina propria	2 (1.03)	19 (17.76)	
Muscularis mucosae	4 (2.05)	17 (15.89)	
Submucosa	13 (6.67)	24 (22.43)	
Muscularis propria	16 (8.21)	11 (10.28)	
Serosa	103 (52.82)	27 (25.23)	
Subserosa	57 (29.23)	9 (8.41)	

Table 3

The tumor characteristics of enrolled patients

	Type 1 (*n* = 195)	Type 2 (*n* = 107)	*P* value
SRC proportion			0.880
Pure SRC	23 (11.79)	12 (11.21)	
PDAC + SRC	172 (88.21)	95 (88.79)	
Blood vessels invasion	94 (48.21)	21 (19.63)	<0.001
Nerve invasion	112 (57.44)	37 (34.58)	<0.001
Lymph node invasion	161 (82.56)	49 (45.79)	<0.001
Lymph node metastasis sites			
Cardia*	10 (5.13)	1 (0.93)	0.124
Lesser curvature	57 (29.23)	13 (12.15)	0.001
Greater curvature	33 (16.92)	6 (5.61)	0.005
Gastric sinus	16 (8.21)	6 (5.61)	0.406
Hepatogastric space	39 (20.00)	3 (2.80)	<0.001
Retroperitoneum	26 (13.33)	4 (3.74)	0.008
pT stage			<0.001
Tis	0 (0.00)	2 (2.02)	
T1	14 (9.33)	54 (54.55)	
T2	13 (8.67)	15 (15.15)	
T3	57 (38.00)	15 (15.15)	
T4	66 (44.00)	13 (13.13)	
pN stage			<0.001
N0	44 (29.33)	67 (67.68)	
N1	37 (24.67)	14 (14.14)	
N2	35 (23.33)	8 (8.08)	
N3	34 (22.67)	10 (10.10)	
Distant metastasis	45 (23.08)	8 (7.48)	0.001
Distant metastasis sites			
Liver	7 (3.59)	1 (0.93)	0.317
Peritoneum*	32 (16.41)	3 (2.80)	<0.001
Uterus and ovaries†	6 (3.06)	0 (0.00)	0.093
Bone†	6 (3.08)	1 (0.93)	0.428
Pancreas†	3 (1.54)	1 (0.93)	1.000
Lung†	4 (2.05)	0 (0.00)	0.301
Adrenal gland†	3 (1.54)	0 (0.00)	0.555

PDAC + SRC: Poorly differentiated carcinoma with signet ring cell component; SRC: Signet ring cell.

*Corrected χ^2 test.

†Fisher precision probability test.

for deficient DNA mismatch repair (dMMR) additionally. The prevalence of dMMR was 3.57% (3/84) in the present study. Specifically, the deficiencies of MSH6, MSH2, MLH1, and PMS2 were observed in 1 (1/84, 1.19%), 1 (1/84, 1.19%), 3 (3/84, 3.57%), and 3 (3/84, 3.57%) cases, respectively. Nevertheless, two patients (2/84, 2.38%) presented a codeficiency of MLH1-PMS2. One patient (1/84, 1.19%) developed four mismatch repair protein deficiencies concurrently. It is worth noting that all dMMRs were observed in type 1 patients. This is probably the most important distinction from type 2 patients.

Treatment selections

In terms of treatment selection, the majority of the enrolled patients received surgical intervention along with perioperative chemotherapy or immunotherapy. Particularly, a higher proportion of type 1 patients in the present study received preoperative chemotherapy ($P < 0.001$) and preoperative immunotherapy ($P = 0.015$). In contrast, more patients of type 2 (92.52%) received surgical intervention ($P < 0.001$). Additionally, there was a notable disparity in the surgical approach between the two endoscopic ultrasonographic manifestations ($P < 0.001$). More patients of type 2 received subtotal gastrectomy, whereas a higher proportion of type 1 patients underwent total gastrectomy. In terms of postoperative therapy, a higher proportion of type 1 patients received postoperative chemotherapy (46.67% vs 28.04%, $P = 0.002$; Table 5).

DISCUSSION

The object of the present study was to explore the disparities in clinicopathological characteristics of GSRCC patients confirmed by pathological examination based on distinct endoscopic ultrasonographic manifestations. Our findings revealed that type 1 patients were more frequently associated with larger tumors, thicker walls of the involved stomach, and deeper tumor invasion as observed under EUS. Moreover, a higher proportion of type 1 patients exhibited affected blood vessel, nerve, lymph node, and peritoneal metastasis. Notably, all cases of dMMR were observed in type 1 patients.

GSRCCs tend to exhibit larger tumor size and deeper tumor invasion compared with other types of gastric cancer.[15] Our study identified statistically significant disparities in tumor size and affected gastric wall thickness between the type 1 and type 2 patients under EUS. In terms of tumor invasion depth, our results revealed that type 1 patients exhibited a tendency toward deeper tumor invasion, with more than 50% of the tumors infiltrating into the serosal layer. Conversely, type 2 patients showed a more even distribution of tumors across all hierarchies of the gastric wall. Previous study confirmed that GSRCCs exhibit varying rates of invasion at different layers of gastric wall, with a relatively slower rate within the mucous and submucosal layers, but a fast rate once it breaks through the submucosa.[16] Therefore, we believe that the differences in invasion speed across different layers of the gastric wall

Table 4

The serological test and immunohistochemical examination results of enrolled patients

	Type 1 (*n* = 195)	Type 2 (*n* = 107)	*P* value
Tumor markers			
CEA elevation (>5 μg/L)	27 (13.85)	4 (3.74)	0.006
CA-125 elevation (>35.0 U/mL)*	13 (6.67)	1 (0.93)	0.048
CA-19.9 elevation (>37.0 U/mL)	15 (7.69)	2 (1.87)	0.036
CA-7.24 elevation (>6.9 U/mL)	18 (9.23)	2 (1.87)	0.014
Decreased hemoglobin (<130 g/L)	101 (51.79)	30 (28.04)	<0.001
PCK positive	101 (59.76)	66 (65.35)	0.361
HER2			0.233
0	95 (60.13)	64 (67.37)	
1+	47 (29.75)	24 (25.26)	
2+	15 (9.49)	7 (7.37)	
3+	1 (0.63)	0 (0.00)	
MMR-IHC	63	21	
Loss of MSH6†	1/63 (1.59)	0 (0.00)	1.000
Loss of MSH2†	1/63 (1.59)	0 (0.00)	1.000
Loss of MLH1†	3/63 (4.76)	0 (0.00)	0.570
Loss of PMS2†	3/63 (4.76)	0 (0.00)	0.570

CA-125: Carbohydrate antigen 125; CA-19.9: Carbohydrate antigen 19.9; CA-7.24: Carbohydrate antigen 7.24; CEA: Carcinoembryonic antigen; HER2: Human epidermal growth factor receptor 2; MMR-IHC: Immunohistochemical examination for mismatch repair proteins; PCK: Phosphoenolpyruvate carboxykinase.

*Corrected χ^2 test.

†Fisher precision probability test.

Table 5

The treatment selections of enrolled patients

	Type 1 (n = 195)	Type 2 (n = 107)	P value
Treatment			
Preoperative chemotherapy	63 (32.31)	9 (8.41)	<0.001
Preoperative radiotherapy*	4 (2.05)	1 (0.93)	0.659
Preoperative immunotherapy†	13 (6.67)	0 (0.00)	0.015
Surgical intervention	150 (76.92)	99 (92.52)	<0.001
Surgical type			<0.001
Total gastrectomy	71 (47.33)	24 (24.24)	
Subtotal gastrectomy	79 (52.67)	75 (75.76)	
Postoperative chemotherapy	91 (46.67)	30 (28.04)	0.002

*Fisher precision probability test.

†Corrected χ^2 test.

may contribute to the observed variations in tumor invasion distribution between the two types of endoscopic ultrasonographic manifestations.

It is worth noting that the aforementioned findings seem to imply that the two distinct endoscopic ultrasonographic manifestations (type 1 and type 2) may represent different stages of disease progression, respectively. Significant differences between the two distinct endoscopic ultrasonographic manifestations were observed in clinicopathological characteristics including symptoms, laboratory test results, examination findings, and treatment decisions. Type 1 patients experienced more weight reduction throughout the progression of disease, a higher prevalence of elevated levels of carcinoembryonic antigen, CA-125, CA-19.9, and CA-7.24 and were more likely to develop anemia. Additionally, type 1 patients showed a higher prevalence of affected blood vessels, nerves, lymph nodes, distant metastasis, and peritoneal metastasis.

However, no significant difference in the course of disease was found between the distinct endoscopic ultrasonographic manifestations. Besides, approximately one-third of type 2 patients in the present study displayed tumor invasion extending deep into the serosa and subserosa, despite the presence of an intact hierarchical structure of the gastric wall under EUS. This finding suggests that tumor invasion in type 2 patients can be deceptive, as it may not be readily apparent based solely on the EUS findings of the gastric wall. Taken together, it becomes evident that the two distinct endoscopic ultrasonographic manifestations of GSRCCs do not simply reflect variations between early and advanced stages of the disease. Instead, they were likely to represent two separate clinical subtypes with distinctive features. The differences observed in clinicopathological characteristics indicate that type 1 and type 2 GSRCCs have distinct clinical presentations and behavior. Further research is warranted to explore the underlying molecular and genetic factors that contribute to these variations and to ascertain the implications for treatment and prognosis.

The prevalence of dMMR in GSRCC has been reported to range from 0% to 33%, which aligns with the results of the present study.[17] Although no significant difference was found between the two types of endoscopic ultrasonographic manifestations, it is noteworthy that all cases of dMMR were found exclusively in type 1 patients. These findings suggest that a certain amount of tumors in type 1 patients may possess higher immunogenicity, making them more susceptible to be recognized and attacked by the immune system. Additionally, these tumors may exhibit greater sensitivity to immunotherapy. Further study is needed to explore the underlying mechanisms behind this observation and to assess the potential implications for immunotherapeutic approaches in type 1 GSRCC patients.

The current study also identified differences in treatment selections between patients of type 1 and type 2 endoscopic ultrasonographic manifestations. More patients of type 1 opted for perioperative chemotherapy, whereas those of type 2 tended to choose surgical intervention. These differences in clinicopathological characteristics between the two endoscopic ultrasonographic manifestations likely contribute to the variation in treatment decision-making. In addition, a notable disparity was observed in the surgical approach between the two groups. Contrary to the previous recommendation for standard total gastrectomy in patients with GSRCC,[18] a higher proportion of type 2 GSRCC patients underwent subtotal gastrectomy. Despite the differences in treatment selections observed in the present study, no statistically significant difference in prognosis was found (not shown in the results). However, further research is necessary to identify more effective interventions for GSRCC, taking into account the distinct endoscopic ultrasonographic manifestations and their associated clinicopathological characteristics.

The present study has certain limitations. First, as a retrospective study, there is a possibility of recall bias. Second, the limited sample size and absence of long-term follow-up in this study may potentially undermine the strength of support for the present conclusion. Therefore, conducting multicenter prospective studies with long-term follow-up is imperative to further elucidate the findings of this study.

In conclusion, the present study provides a comprehensive summary of the clinical profiles of individuals with GSRCC based on the distinct endoscopic ultrasonographic manifestations. Current results provide valuable insights into the clinicopathological characteristics of patients with distinct endoscopic ultrasonographic manifestations to facilitate clinical decision-making. Moreover, the current findings suggest that those two endoscopic ultrasonographic manifestations may represent different subtypes of GSRCC, highlighting the need for further researches to explore the differences in diagnostic and management strategies.

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Conflicts of Interest

The authors declare that they have no financial conflict of interest with regard to the content of this report.

Author Contributions

Chaoqun Han, Zhen Ding, and Rong Lin designed the research. Shanshan Liu conducted the research. Chaoqun Han, Guochen Shang, Jun Liu, and Yu Jin analyzed the data. Shanshan Liu and Chaoqun Han wrote the paper. Zhen Ding and Rong Lin had primary responsibility for the final content. All authors read and approved the final manuscript.

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