ORIGINAL ARTICLE

Risk factors for the failure of endoscopic resection of gastric submucosal tumors: a long-term retrospective case–control study

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Abstract

Objective Endoscopic resection (ER) is an effective treatment method for gastric submucosal tumors (G-SMTs), but endoscopic resection failure requires emergency surgery. The purpose of this study was to assess potential risk factors for endoscopic resection failure.

Methods A total of 1041 patients with G-SMT undergoing endoscopic resection were enrolled. Twenty-five patients in whom endoscopic resection failed, requiring a transition to surgery midway through the operation, were included in the failed group, and 1016 patients who received successful endoscopic resection were included in the successful endoscopic resection group. Baseline and lesion characteristics were recorded, and the differences in tumor characteristics and risk factors for resection failure of G-SMT were analyzed. Sensitivity analysis was performed to detect the stability of the indicator.

Results Of the 1041cases included, there were 25 cases (2.4%) of failed endoscopic resection. Binary logistic analysis showed that the independent risk factors included tumors originating from deep muscularis propria(OR = 14.42, 95% CI 4.47–46.52), size > 3 cm (OR = 7.75, 95% CI 2.64–22.70), exophytic growth pattern (OR = 4.98, 95% CI 1.62–15.29), endoscopist with less experience (OR = 5.99, 95% CI 1.07–12.19), and irregular borders (OR = 4.13, 95% CI 1.40–12.19). The stable risk factors were tumors size, tumor origin and growth pattern according to sensitivity analysis.

Conclusions Tumors originating from the deep muscularis propria, tumor size > 3 cm, endoscopists with less experience, an exophytic growth pattern, and irregular boundaries were found to be independent risk factors for endoscopic resection failure. To reduce the risk of endoscopic resection failure, physicians should carefully evaluate G-SMT characteristics preoperative.

Keywords Gastric submucosal tumors · Endoscopic resection · Risk factors · Case–control study

Introduction

Gastric submucosal tumors (G-SMTs) refer to tumors that originate below the gastric mucosal layer, mainly including gastrointestinal stromal tumors (GISTs), neurogenic tumors, leiomyomas and lipomas. Most of them have no

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clinical symptoms and are incidentally detected during upper endoscopic examination; however, the malignant transformation of GISTs, the most frequent gastric mesenchymal neoplasm arising from the muscularis propria (MP) of the stomach, can occur in up to 10–30% of cases [1–5]. Some benign tumors can also cause abdominal pain, bleeding and other clinical manifestations. According to the guidelines established by the National Comprehensive Cancer Network (NCCN), resection is the first-line treatment for nonmetastatic GISTs > 2 cm. However, GISTs < 2 cm that lack high-risk features upon endoscopic ultrasound (EUS) only require monitoring and follow-up every 1–2 years [6]. Unfortunately, long-term follow-up can make patients feel anxious, and even GIST tumors < 2 cm with < 5 mitoses/50 high-power fields (HPF) can metastasize, although it is rare [7, 8].

Endoscopic resection (ER) is a minimally invasive treatment that is characterized by less trauma, a high overall resection rate, quick postoperative recovery, few adverse events and excellent long-term results [9–11]. In addition, ER can achieve similar oncological outcomes as surgical treatment for G-SMTs less than 5 cm in size [12, 13]. Most G-SMTs do not cause lymph node metastasis [14–16] and can be removed directly without the need for lymph node dissection. Thus, ER has become a suitable choice for the treatment of small G-SMTs [17, 18].

However, the accurate assessment of surgical indications and the complete resection rate still have important clinical significance for G-SMT patients who undergo ER [19]. Preoperative evaluations such as endoscopy, ultrasound endoscopy (EUS), and computed tomography (CT) assessment are useful for avoiding clinical misjudgments and in guiding G-SMT treatment strategies [20–23]. With the continuous expansion of the indications for the ER of G-SMTs [24], more challenging cases of G-SMTs have been attempted, and ER failure has become an emerging issue. In these cases, emergency surgery is required to manage bleeding or even to save the patient's life. This situation not only increases medical risks but also increases the patient burden. The combination of EUS and CT examination before ER could allow for a more reliable preoperative assessment of the risk factors for ER failure. However, to date, few studies have analyzed the risk factors for ER failure in G-SMT patients. Thus, we performed this study to summarize the characteristics of G-SMT patients who underwent ER from 2013 to 2020 at our hospital and aimed to identify reliable risk factors for ER failure in these patients.

Materials and methods

Patient recruitment

This study was a retrospective case–control study. A total of 1041 G-SMT patients who underwent ER in the Department of Gastroenterology, the First Affiliated Hospital of Nanjing Medical University, from January 2013 to December 2020 were included (Fig. 1). This work was approved by the Ethics Committee of the First Affiliated Hospital of Nanjing Medical University (2021-SR-449).

Patients diagnosed with G-SMTs who underwent ER were considered for inclusion. The principal inclusion criteria were as follows: (1) tumors originating from the MP according to EUS; (2) no evidence of lymph node involvement, intraperitoneal implantation or distant metastasis; and (3) written informed consent to undergo ER. Exclusion criteria were as follows: (1) patients with nonneoplastic lesions; (2) patients with missing data. All patients without

any coagulation dysfunction and could tolerate anesthesia intubation.

Standard definitions were used, as follows: ER failure: The tumor could not be removed by ER (including ESD and EFTR), and the patient required emergency surgery for further surgical remediation. Successful ER: The tumor could be completely removed by ER.

The groups and selection strategy were as follows: The case group included patients who experienced ER failure. A total of 25 patients were included in this group through the continuous enrollment method. The control group included patients who successfully underwent ER. A total of 1016 patients were included in this group through the continuous enrollment method. The 1041 G-SMTs included GISTs (709 cases), leiomyomas (106 cases), heterotopic pancreas (82 cases), lipomas (76 cases), neuroendocrine tumors (17 cases), schwannomas (12 cases), glomus tumors (8 cases) and others (31 cases). Except for one neuroendocrine tumor (G3), most of the other tumors were benign, and this patient underwent additional surgery.

## Surgical instruments, surgical methods and pathological examinations

Instruments

The instruments used included an electronic gastro-scope (Olympus GIFQ260J), dual channel endoscopy (Olympus GIF-2T0260M), radial-scanning echo endoscopy unit (Olympus UM 240), ultrasonic micro probe (OlympusUM-2R), linear array endoscope (EG-3830, Pentax), color doppler ultrasound (Hitachi Vision Avius L, Japan), IT knife (Olympus KD-611L), dual knife (Olympus KD-650Q/L), single use injector (Olympus NM-400L-0423), electrosurgical hemostatic forceps (Olympus FD-410LR), disposable electrosurgical snare (Olympus SD-210U-25), metal clamp (micro-tech (Nanjing) ROCC-D-26-195-C), rotatable grasping forceps (Olympus FG-44NR-1), endoloop (MAJ-254; Olympus), ERBE electric cutting device and CO2 gas pump, micro probe (Olympus UMDP12-25R), etc.

Endoscopic resection methods

ER was performed in all cases under intravenous anesthesia and with tracheal intubation. The patients were placed in the left decubitus position for all procedures.

Endoscopic ultrasonography (EUS) was used to record the echo intensity, echo uniformity, origin level, and tumor size. The superficial MP layer was defined as the upper half of the fourth layer with the tumor capsule located in the upper half of the fourth layer. The deep MP layer was defined as the lower half of the fourth layer with the tumor

LECS: Laparoscopy and Endoscopy Cooperative Surgery
SAER: Snare-assisted endoscopic resection
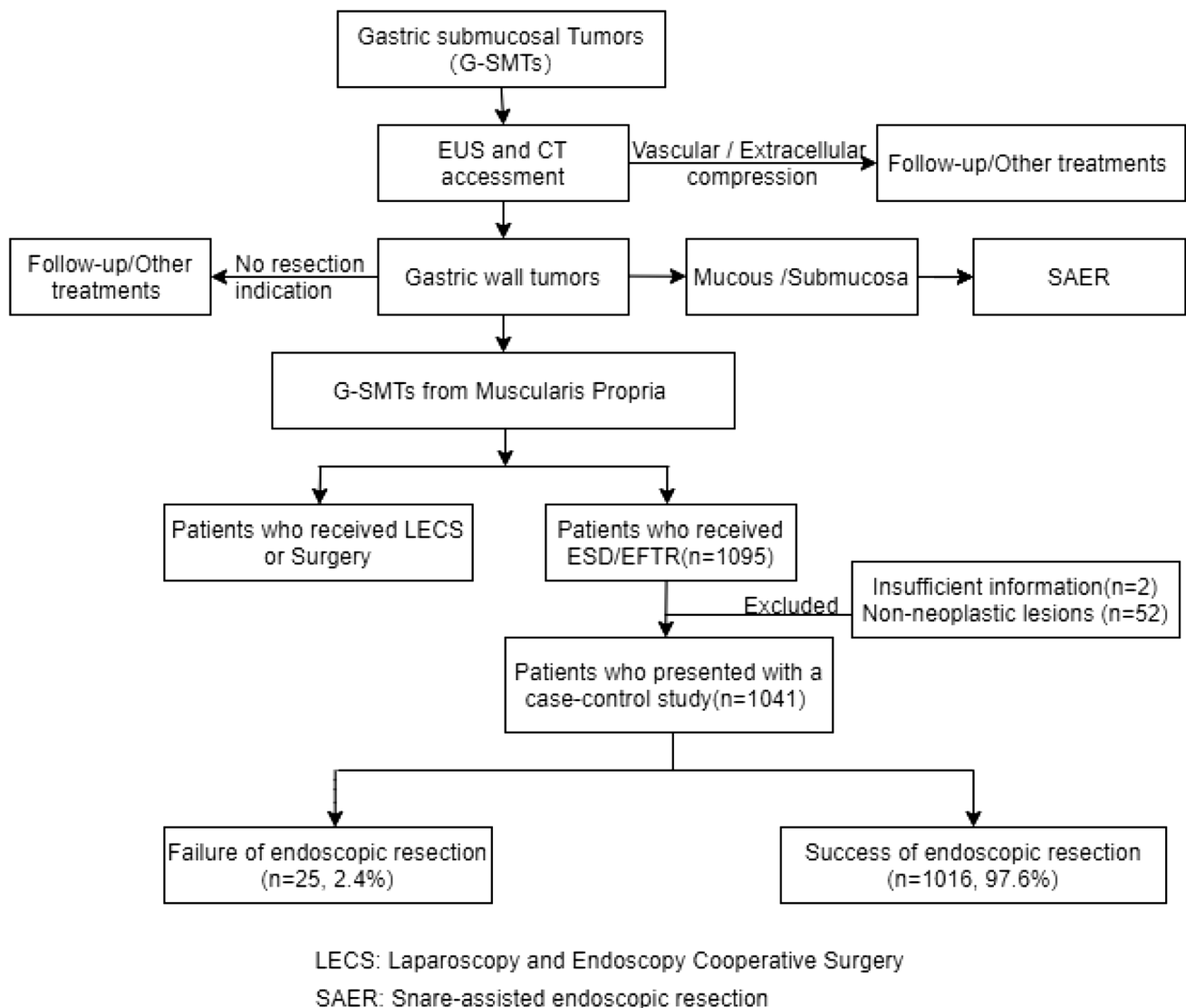
Fig. 1 Diagnosis and treatment process of G-SMTs and schematic of this study design

capsule located in the lower half of the fourth layer or tightly adhered to the fifth layer [20].

Endoscopic submucosal dissection (ESD) was performed according to Xin-gang Shi et al. [24]: Marking dots were placed around the tumors with an argon plasma coagulation (APC)/dual knife, and a submucosal injection of 100 ml saline + 2 ml indigo carmine + 1 ml adrenaline was administered near the marking dots. A dual knife was used to cut around the lesion to the submucosa. The submucosal layer was dissected until the tumor was exposed. Separation was continued until the tumor was completely removed while keeping the MP layer intact. After hemostasis on the wound surface was performed with hot forceps, the wound surface was clamped by metal clips.

For endoscopic full-thickness resection (EFTR) [24], marking dots were placed, cuts were made around the dots,

and then submucosal layer dissection was performed in the same manner as in the ESD procedure. When the tumor was located in the deep MP layer or close to the serosa, a circumferential incision into the serous membrane around the tumor was performed with an IT knife, and an "artificial" perforation was made. Metal clips were used to close the wound surface in some easy cases.

For patients with SMTs originating from deep MP or exophytic growth, the "traction" method was necessary [25, 26]. The main "traction" method used is described as follows: Using a dual-channel endoscopy to perform ER, rotatable grasping forceps and a snare were placed separately using the two channels. The snare was enlarged and anchored to the bottom of the SMT, and then rotatable grasping forceps were used to grasp the tumor before the final resection cut. Thus, the tumor could be freed from the GI wall while

preventing it from falling into the peritoneal cavity (Fig. 2). For cases with defects larger than 20 mm, a purse-string suture is usually required, as follows [27–29]: an endoloop is made, and clips are placed at the proximal edge of the defect, with the endoloop anchored by the endoclips at the edges around the defect. After the endoloop is tightened, the wound surface is closed simultaneously from the rim to the center. Additional clips can be placed to obtain complete wound closure if necessary. If a pneumoperitoneum develops, a 20-gauge needle can be used to insect into the right lower quadrant to release gas [30].

Postoperative pathology

The excised specimens were fixed with neutral formalin and sent for pathological examination and immunohistochemical staining. All tissues were stained with hematoxylin–eosin (HE) in the pathology department of our hospital. Patients with gastric stromal tumors were subjected to immunohistochemical methods to determine the expression of CD34, CD117, DOG-1, SMA, S-100, Desmin, and Ki-67 and the mitotic figure count to further clarify the pathological diagnosis and assess the degree of risk.

Research methods

General patient data were retrieved from the electronic medical record HIS system, which included sex, age, and other hospitalization information.

Other data collected herein included (1) the origin layer of the G-SMTs (superficial MP/deep MP); (2) the tumor location (fundus, greater/lesser curvature, anterior/posterior side); (3) the tumor size (the maximum cross-sectional diameter of the tumor was divided according to a size of ≥ 3 cm or < 3 cm); (4) ultrasonic echo characteristics (high/low, uniform/nonuniform); (5) growth pattern, namely, intraluminal growth versus exophytic growth (intraluminal growth means that $> 50\%$ of the tumor body protrudes into the lumen under EUS and/or CT evaluation, while exophytic growth means that $> 50\%$ of the tumor protrudes out of the lumen under EUS and/or CT evaluation); (6) boundary (regular or irregular); and (7) endoscopist experience level (endoscopists are considered to be experienced after performing more than 40 ESD cases independently, because adverse events related to ESD were found to be significantly reduced after 40 cases [31]).

The growth pattern was defined according to CT examination. Exophytic growth pattern accounted for over half of
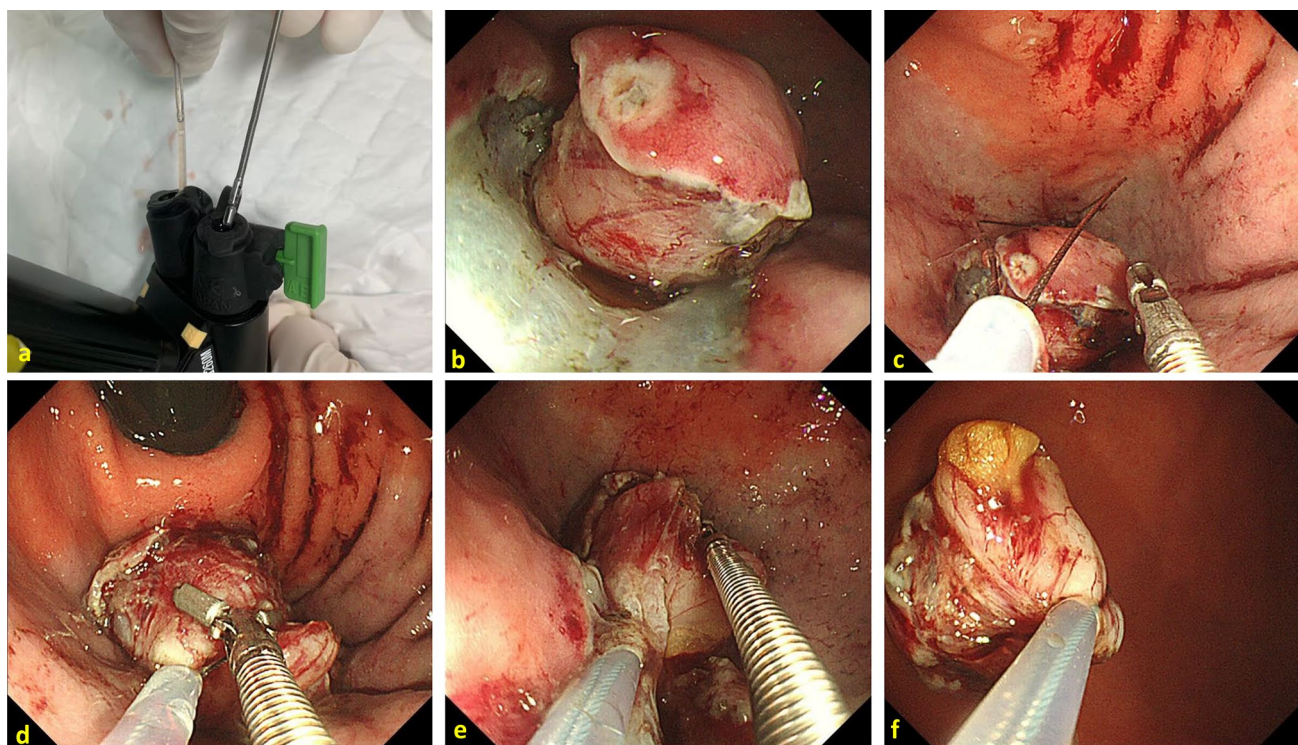
Fig. 2 Complete tumor resection assisted by the "traction" method. **a** Foreign-body forceps and snares were inserted through the double cavity mirror channel. **b** SMT of the gastric fundus was separated to the serosa layer, and perforation occurred. **c** Snare was opened, and the foreign-body forceps were ready. **d**, **e** Foreign-body forceps were used to grasp the tumor, lift or push it to fully expose the bottom of the tumor, and then the snare was tightened and the tumor was removed. **f** Tumor was removed from the body

the SMT outside the radian of gastric wall. Otherwise, it was classified as intraluminal growth pattern. The tumor origin was defined according to EUS when tumor size was less than 2 cm (Fig. 3). However, for those G-SMTs larger than 2 cm, the muscularis propria was almost completely occupied by the tumor; therefore, tumor origin was decided based on CT. In these cases, the intraluminal tumor was classified as originating from the superficial-MP and the exophytic tumors were defined as deep-MP.

Statistical analysis

Data analysis was performed with SPSS 26.0 statistical software package (SPSS Inc, Chicago, Illinois, USA). The tumor characteristics of the case group and control group were compared, and the characteristics of the G-SMT patients in each group based on the success and failure of the operation were analyzed. The variables with $P \leq 0.1$ in the univariate analysis were incorporated into the multivariate model. Multivariate logistic regression analysis was used to detect the relationship between surgical failure and G-SMT characteristics and to calculate the odds ratio and 95% confidence interval. The dependent variables were the success of ER and the failure of ER, and the independent variables were tumor lesion location, size, level of origin, irregular boundaries, ultrasonic echo characteristics and doctor experience. $P < 0.05$ was considered statistically significant.

Considering possible reverse causality, we conducted a sensitivity analysis by excluding subjects whose receive endoscopic resection during the first 2 years. Furthermore, we conducted further sensitivity analysis to investigate whether endoscopists' experience affect the risk of endoscopic resection.

Results

Flow chart

A total of 1095 tumors originating from the submucosa and muscularis propria were treated with ER (Fig. 1). Of those, 54 patients were excluded, 2 patients without sufficient information, and 52 patients were diagnosed with nonneoplastic lesions after ER. Therefore, 1041 patients were ultimately included in this case–control study.

Baseline characteristics of the subjects and clinicopathological characteristics of lesions

The baseline and clinicopathological characteristics of the study subjects and lesions are shown in Table 1. The mean age of the patients was 65.9 ± 11.3 years, and 62.6% were female. Among them, 1041 had G-SMTs, with 562 (54.0%) located in the fundus, 340 (32.9%) located in the greater/lesser curvature and 137 (13.1%) located on the anterior/posterior side. The mean diameter was 1.54 ± 1.04 cm, and most tumors had a diameter of ≤ 3 cm (87.7%). In the control group, the mean size was 1.50 ± 0.99 cm (range, 0.4 cm to 5 cm). In the research group, the median size was 3.30 ± 1.36 cm (range, 1.2 cm to 6 cm). A total of 985
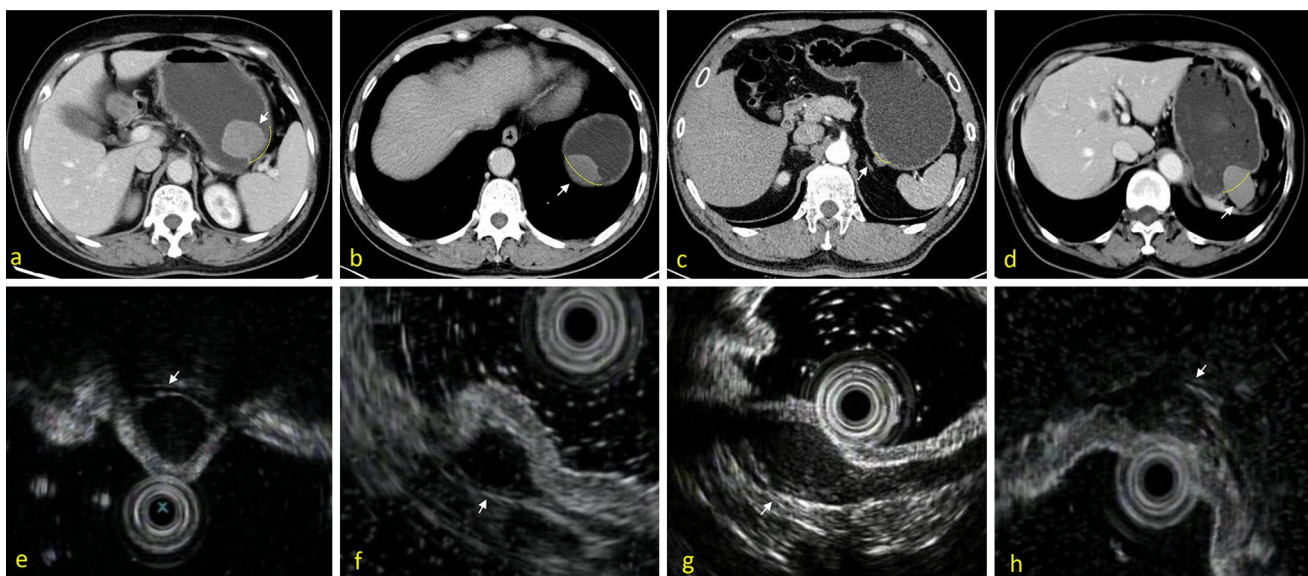
Fig. 3 **a**, **b** Endoluminal growth pattern: CT scan showed dominant tumor located in the gastric cavity; **c**, **d** Exophytic growth pattern: CT scan showed dominant tumor was outside the gastric cavity; **e–g** Superficial-MP tumor: endoscopic ultrasound shows tumor capsule was in the upper half of the mucosal propria layer; **h** deep-MP tumor: endoscopic ultrasound showed tumor capsule tightly adhered to the serosal layer

Table 1 Research objects and clinicopathological characteristics of lesions

	$N = 1041$
Age (mean ± SD)	65.9 ± 11.3
Sex	
Male	389 (37.4%)
Female	652 (62.6%)
Tumor location	
Gastric fundus	562 (54.0%)
Greater/Lesser curvature	340 (32.7%)
Anterior/posterior sides	137 (13.2%)
Tumor size	
≤ 3 cm	917 (88.1%)
> 3 cm	124 (11.9%)
Ultrasonic echo characteristics	
High	39 (3.7%)
Low	1002 (96.3%)
Uniform	1008 (96.8%)
Non-uniform	33 (3.2%)
Layer of origin (muscularis propria)	
Superficial	913 (87.7%)
Deep	128 (12.3)
Dominant growth pattern	
Endoluminal	985 (94.6%)
Exophytic	56 (5.4%)
Irregular borders	
Yes	79 (7.6%)
No	962 (92.4%)
Endoscopists	
Experienced	1012 (97.2%)
Less experienced	29 (2.8%)

patients were classified as having superficial MP (97.2%), and 128 were classified as having deep MP (12.3%) according to the relationship between tumor location and the MP layer by EUS examination. Tumor borders in 962 patients (92.4%) were irregular. The dominant growth pattern was intraluminal (94.6%). In addition, 97.2% of the procedures were performed by experienced endoscopists.

G-SMTs with endoscopic resection (ER) failure

ER failure occurred for 25 G-SMTs (Table 2). The main reasons for ER failure included serous membrane damage or adhesions (60%), exophytic growth (52%), intraoperative bleeding (52%), and a large tumor size (20%). There were 3 cases (12%) of tumors less than 2 cm in size and 17 cases (68%) of tumors larger than 3 cm. In one case, the tumor was located in the cavity and had a regular shape, but it was difficult to control intraoperative bleeding due to the abundance of tumor vessels. On the other hand, tumors that

extensively adhere to extragastric structures can also cause ER failure. In addition, the actual tumor size during ER was found to larger than that evaluated prior to surgery in a few cases, especially for schwannoma, which was another reason for failure. ER failure occurred for all 6 cases of schwannoma and was related to unclear demarcation between the tumor and muscle, the large base of the tumor and serous membrane damage (Fig. 4). A total of 12 G-SMTs in the failure group had irregular borders, and 5 cases (41.7%) were schwannoma and 7 cases (58.3%) were GIST (Fig. 5).

Risk factors for ER failure

We analyzed the risk factors for ER failure by univariate analysis. The results showed that the tumor growth pattern (OR = 35.671, 95% CI 15.110–84.211), size (OR = 18.053, 95% CI 7.610–42.827), layer of origin (OR = 33.630, 95% CI 12.371–91.422), irregular boundaries (OR = 13.075, 95% CI 5.742–29.769), echo uniformity (OR = 11.567, 95% CI 4.280–31.264) and endoscopist's level of experience (OR = 5.192, 95% CI 1.462–18.444) were related to ER failure (all $P < 0.05$) (Table 3).

Binary logistic regression was performed on all of the above variables showing significant differences in univariate analysis, and the risk factors found to affect ER failure were determined through the regression pattern. The results of the multivariate analysis showed that independent risk factors for ER failure included tumors originating from a deep MP layer (OR = 14.42, 95% CI 4.47–46.52, $P < 0.001$), tumor size Φ > 3 cm (OR = 7.75, 95% CI 2.64–22.70, $P < 0.001$), exophytic growth pattern (OR = 4.98, 95% CI 1.62–15.29, $P = 0.005$), endoscopists with less experience (OR = 5.99, 95% CI 1.07–12.19, $P = 0.042$), and irregular borders (OR = 4.13, 95% CI 1.40–12.19, $P = 0.010$). Of these, the most significant independent risk factor was tumors originating from a deep MP layer, yielding an ER failure rate 14.422 times that of tumors originating from a superficial MP layer (Fig. 4).

ROC curve analysis of independent diagnostic value indicators

According to the result of multivariate Logistic regression analysis, the diagnostic value of risk factors for endoscopic resection failure was evaluated by constructing ROC curve. The result showed that combination of tumor size, layer of origin, dominant growth pattern, irregular borders and endoscopists' experience indicators had high predictive value, with an AUC of 0.953 (95% CI 0.901–1.000). Separately, tumor size, layer of origin, dominant growth pattern and irregular border have moderate predictive value for endoscopic treatment, while the diagnostic performance of endoscopists' experience was less satisfactory

Table 2 G-SMT cases of failed endoscopic resection

No	Age Sex	Lesion location	Tumor size (mm)	Layer of origin	Ultrasonic characteristics	Growth pattern	Borders	Failure/Suspend reason				Pathology type
								Larger tumor diameter	Exophytic growth pattern	Serosa adhesion /damage	Hemorrhage	
1	70 male	Greater/Lesser curvature	50	Deep	Low/Non-Uniform	Exophytic	Regular		•	•		GIST
2	47 male	Anterior/posterior sides	20	Deep	Low/Uniform	Exophytic	Regular		•	•		Schwannoma
3	77 female	Gastric fundus	25	Deep	Low/Uniform	Exophytic	Regular		•	•		GIST
4	51 Female	Greater/Lesser curvature	20	Deep	Low/Uniform	Exophytic	Regular		•			Glomus tumor
5	76 male	Gastric fundus	40	Shallow	Low/Uniform	Endoluminal	Irregular	•			•	GIST
6	64 female	Gastric fundus	60	Deep	Low/Uniform	Endoluminal	Irregular		•	•		GIST
7	63 male	Greater/Lesser curvature	40	Deep	Low/Non-Uniform	Exophytic	Regular		•			GIST
8	76 female	Gastric fundus	40	Deep	Low/Non-Uniform	Exophytic	Irregular	•		•		Schwannoma
9	63 female	Gastric fundus	20	Deep	Low/Uniform	Exophytic	Irregular		•	•		GIST
10	51 male	Gastric fundus	50	Shallow	Low/Uniform	Endoluminal	Irregular	•			•	GIST
11	50 female	Greater/Lesser curvature	30	Deep	Low/Uniform	Exophytic	Irregular		•	•		Schwannoma
12	67 Female	Gastric fundus	30	Shallow	Low/Non-Uniform	Endoluminal	Irregular					GIST
13	78 male	Gastric fundus	35	Shallow	Low/Non-Uniform	Exophytic	Irregular			•	•	GIST
14	42 male	Greater/Lesser curvature	60	Deep	High/Uniform	Exophytic	Regular		•	•	•	GIST
15	57 male	Greater/Lesser curvature	30	Deep	Low/Uniform	Exophytic	Irregular	•	•	•	•	Schwannoma
16	68 male	Anterior/posterior sides	30	Deep	Low/Uniform	Exophytic	Regular		•	•	•	Glomus tumor
17	51 female	Greater/Lesser curvature	35	Deep	Low/Uniform	Exophytic	Irregular	•	•	•		Schwannoma
18	42 male	Gastric fundus	50	Shallow	Low/Uniform	Endoluminal	Regular				•	GIST

Table 2 (continued)

No	Age Sex	Lesion location	Tumor size (mm)	Layer of origin	Ultrasonic characteristics	Growth pattern	Borders	Larger tumor diameter	Exophytic growth pattern	Serosa adhesion /damage	Hemorrhage	Pathology type
								Failure/Suspend reason				
19	63 male	Gastric fundus	15	Deep	Low/Uniform	Endoluminal	Regular				●	GIST
20	67 female	Greater/Lesser curvature	15	Deep	Low/Uniform	Exophytic	Irregular		●	●	●	Schwannoma
21	61 female	Greater/Lesser curvature	12	Deep	Low/Uniform	Endoluminal	Regular				●	GIST
22	51 male	Gastric fundus	30	Shallow	Low/Uniform	Endoluminal	Regular				●	GIST
23	47 male	Gastric fundus	45	Deep	Low/Uniform	Endoluminal	Regular				●	GIST
24	60 male	Gastric fundus	40	Deep	Low/Uniform	Endoluminal	Regular			●	●	GIST
25	62 female	Anterior/posterior sides	28	Deep	Low/Non-Uniform	Exophytic	Irregular		●	●	●	GIST
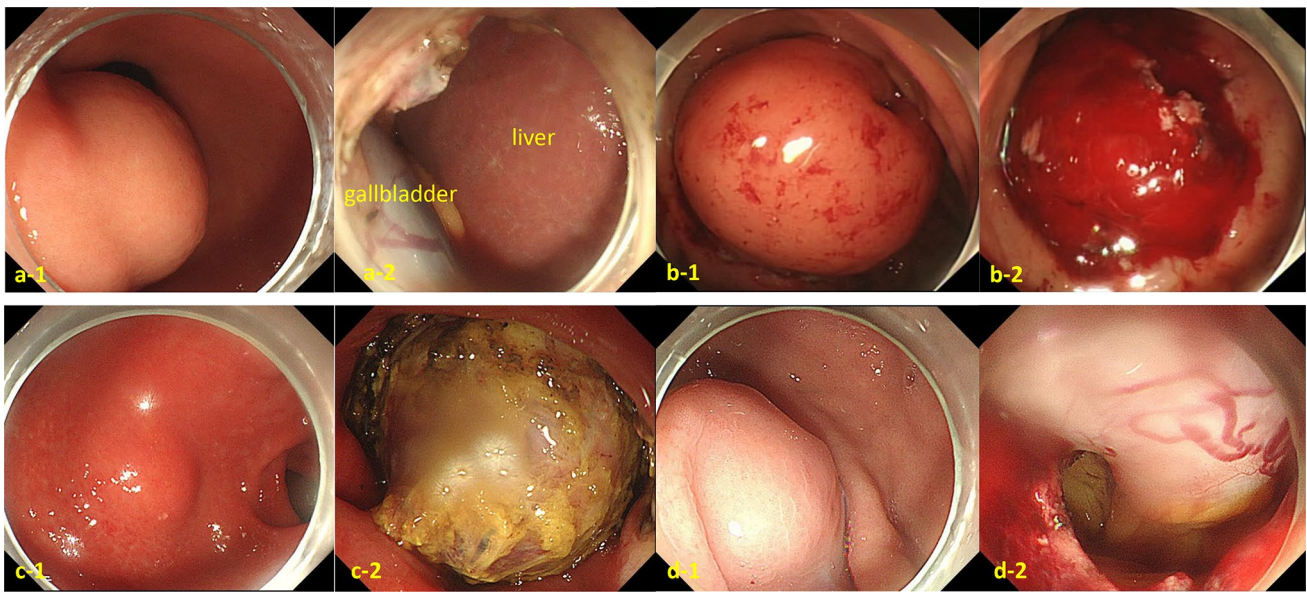
Fig. 4 Partial endoscopic manifestations of the failed endoscopic excision of SMTs. A: Female, 62 years. **a-1** anterior wall of the gastric antrum body junction, 3.0 × 3.0 cm. **a-2** reason for failure of endoscopic excision: adhesion between the tumor and gallbladder. Pathological: GIST, CD34(+), CD117(−), S-100(−), Low risk. B: Male, 47 years. **b-1**, Fundus fornix, 4.0 × 5.0 cm, with ulcer. **b-2**, reason for failure of endoscopic excision: bleeding. Pathological: GIST. CD34 (+), CD117 (+), DGO-1 (+), Low risk. C: Male, 47 years. **c-1**, Anterior wall of the gastric antrum, 2.0 × 2.0 cm, extracavity. **c-2**, reason for failure of endoscopic excision: unclear tumor boundary. Pathological: Schwannoma. D: Female, 77 years. **d-1**, Anterior wall of the gastric antrum, 2.0 × 2.0 cm, extracavity. **d-2**, reason for failure of endoscopic excision: bleeding and adhesion between the tumor and omentum. Pathological: GIST. CD34 (+), CD117 (+), Medium risk
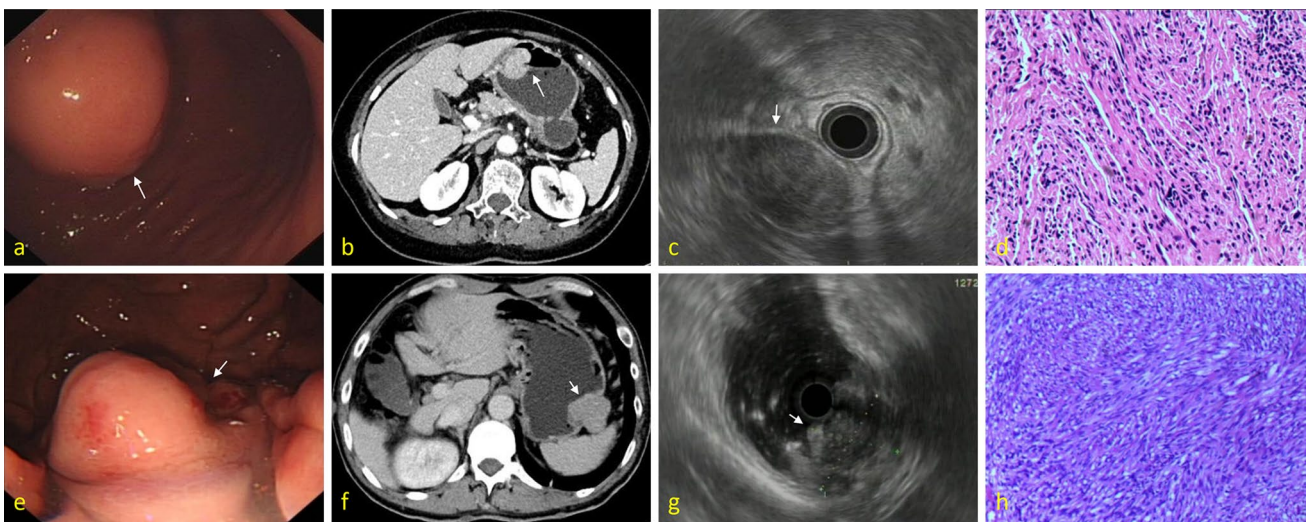
Fig. 5 Gastric submucosal tumors with irregular borders. **a–d** Female, 76 years, gastric fundus, 3.5 × 3.5 cm, with ulcer on surface and an irregular border, hypoechoic changes on EUS, Pathological: schwannoma. **e–h** male, 51 years, gastric fundus, 3.5 × 4.0 cm, with ulcer on surface and an irregular border, uneven echo on EUS. Pathological: GIST, mitotic image < 5/50HPF, CD34(+), CD117(+),DOG-1(+), Low risk

(0.5 < AUC ≤ 0.7). This model presented good goodness of fit by Hosmer and Lemeshow Test ($P = 0.827$).

Sensitivity analysis

Sensitivity analysis results showed that tumor size, tumor origin and growth pattern were similar to the original results,

Table 3 Logistic regression analysis of endoscopic surgery failure

Variable	Univariable analysis coef. (95%CI)	Multivariable analysis coef. (95%CI)	p	
Age (years)	1.04 (1.00, 1.08)	None		
Sex				
Female	Ref.	Ref.		
Male	0.54 (0.25, 1.20)	None		
Tumor Size			<0.001*	
Φ<3 cm	Ref.	Ref.		
Φ≥3 cm	18.05 (7.61, 42.83)	7.75 (2.64, 22.70)		
Tumor Location				
Gastric fundus	Ref.	Ref.		
Greater/Lesser curvature	1.141 (0.483, 2.699)	None		
Anterior/posterior sides	0.945 (0.266, 3.365)	None		
Layer of origin			<0.001*	
Superficial muscularis propria	Ref.	Ref.		
Deep muscularis propria	33.63 (12.37, 91.42)	14.42 (4.47, 46.54)		
Ultrasonic echo characteristics				
Low	Ref.	Ref.		
High	2.30 (0.52, 10.13)	None		
Ultrasonic echo characteristics			0.239	
Uniform	Ref.	Ref.		
Non-uniform	11.57 (4.28, 31.26)	2.51 (0.54, 11.57)		
Dominant growth pattern			0.005*	
Endoluminal	Ref.	Ref.		
Exophytic	35.67 (15.11, 84.21)	4.98 (1.62, 15.29)		
Irregular borders			0.010*	
No	Ref.	Ref.		
Yes	13.08 (5.74, 29.77)	4.13 (1.40, 12.19)		
Endoscopists			0.042*	
Experienced	Ref.	Ref.		
Less experienced	5.19 (1.46, 18.44)	5.99 (1.07, 33.61)		

presenting good stable and reliable. However, irregular borders and endoscopists' experience were different from the original results when excluding cases of the first 2 years of the study. In addition, in the other model, in condition of excluding the case study of inexperienced endoscopists, irregular boundaries was different from the original results (Table 4), indicating irregular borders and endoscopists' experience were not stable enough. This result may be related to the insufficient events.

Discussion

G-SMTs are usually a diagnostic and therapeutic challenge. To date, the most reliable measures are EUS and CT; however, it is sometimes difficult to differentiate subepithelial from mesenchymal tumors and benign from malignant lesions using these modalities. The NCCN guidelines (2016) suggest that patients who have GISTs < 2 cm should undergo periodic endoscopy and/or EUS every 6 months, which will increase the cost of treatment, patient anxiety, and the risks

associated with repeated endoscopic procedures [32]. ER is an endoscopic method used to remove G-SMTs from the stomach wall; this approach not only reduces trauma while providing a histological diagnosis but also allows for complete tumor resection. However, the endoscopic resection of SMTs should be performed only as part of a clinical trial in specialized centers due to the difficulty of operation [32].

When the tumor originates from the deep MP layer, the bottom is usually tightly connected with the muscle layer or serosa, and some tumors even adhere to the tissue outside the gastric wall [33]. Thus, it is quite possible to damage the serosa during tumor dissection, which can result in ER failure [34]. This study found that the ER failure rate increased by 14.422 times when the tumor originated from the deep MP layer, which is consistent with the results of previous studies. In addition, Białek found that patients with submucosal tumors derived from the muscle layer have a lower rate of complete resection with endoscopic mucosal resection (EMR) and have a higher risk of recurrence [35]. In our study, we found that tumors originating from the deep MP layer were more likely to grow extraluminally, thereby

Table 4 Association between G-SMTs characteristics and ER failure in sensitivity analyses

	Model 1	Model 2	Model 3
Case. no	1041	905	1012
Tumor location (ref = Gastric fundus)	0.85 (0.37, 1.96)	0.78 (0.31, 1.98)	0.72 (0.29, 1.77)
Tumor size (ref = Φ < 3)	8.00 (2.70, 23.75)	11.11 (3.10, 39.80)	9.88 (3.03, 32.13)
Ultrasonic echo characteristics (ref = Low)	1.74 (0.15, 20.42)	1.38 (0.08, 23.75)	1.52 (0.12, 19.00)
Ultrasonic echo characteristics (ref = Uniform)	2.33 (0.49, 11.03)	1.56 (0.28, 8.74)	2.05 (0.41, 10.12)
Layer of origin (ref = Superficial)	14.29 (4.41, 46.34)	17.49 (4.73, 64.61)	14.80 (4.20, 52.13)
Dominant growth pattern (ref = Endoluminal)	4.95 (1.58, 15.51)	9.50 (2.72, 33.27)	7.12 (2.16, 23.54)
Irregular borders (ref = No)*	4.23 (1.42, 12.62)	2.84 (0.77, 10.49)	2.92 (0.89, 9.66)
Endoscopists (ref = Experienced)*	5.80 (0.99, 33.85)	5.38 (0.68, 42.60)	None

Model 1: was adjusted for sex and age (continuous)

Model 2: Excluding participants whose treatment with ER surgery in the first 2 years

Model 3: Excluding participants whose treatment with less experienced endoscopists

*Sensitivity analysis results differ from the original results

increasing difficulty of ER. In addition, Won Min showed that G-SMTs with extracavity growth are more likely to be GISTs [36]. As GISTs enlarge, exophytic GISTs may invade adjacent structures, such as the pancreas, colon, or diaphragm [37]. Therefore, endoscopists should always closely monitor such giant tumors.

There are few studies on the relationship between endoscopic resection failure and intraoperative bleeding. In the present retrospective case–control study, 25 patients with G-SMTs experienced ER failure, with intraoperative bleeding being the main reason for failure (52%). In this situation, large nutrient vessels of the G-SMT ruptured, and endoscopic visualization was impacted. Severe hemorrhage may result in uncontrollable abdominal hemorrhage because of defects in the gastric wall. Thus, these patients need to be immediately converted to surgery to manage bleeding, as described in previous reports [38]. ER may be a technically feasible, safe, less invasive and oncologically suitable option for GISTs less than 3 cm [11]. However, GISTs larger than 3 cm in diameter may need to be resected in slices, which could cause greater damage to the serosal layer, increasing not only the difficulty of the operation but also the risk of incomplete resection [39]. Although previous studies have shown that the risk of malignant transformation of GISTs larger than 3 cm is elevated [40, 41], in this study, even GISTs with a diameter of 6 cm were found to be pathologically low risk. On the other hand, some GISTs with a tumor diameter of 2 cm appeared to have a moderate risk of transformation, but none of the 25 G-SMT patients experiencing ER failure were found to have a high risk. Similar to previous reports, even for GISTs with a general malignant potential, the best tumor cutoff value related to tumor progression was found to be merely 1.4 cm [42], which is similar to the 1.7 cm value reported by Lachter et al. [43]. In addition, we found that 6 cases couldn't remove from mouth

after successful ER and need the assistance of laparoscopy to remove tumor through abdominal wall, among them 5 cases were larger than 3 cm.

Hoteya et al. reported that noncurative resection (72.0%) of G-SMTs with a maximum size of more than 3 cm did not result in local recurrence and metastasis, and the prognosis was good [44]. This is why patients are more willing to undergo endoscopic resection for larger G-SMTs. In this study, in cases exhibiting an extracavity growth pattern, most of the tumors measured by preoperative endoscopy in the failed cases were smaller than the true size after surgical resection. Therefore, it is necessary to comprehensively evaluate the true size of the tumor using a combination of endoscopy, EUS and CT. Tumors with irregular borders showed a trend of progressive change. In our study, a total of 12 G-SMTs in the failure group had irregular borders, and 5 cases (41.7%) were schwannoma and 7 cases (58.3%) were GIST. The tumor and the surrounding boundary were not clear during surgical separation in 2 patients, which increased the difficulty of ER and resulted in ER failure. Although 2 patients with GISTs in the ER failure group had regular borders, they had a moderate risk of malignancy. One of them had a tumor smaller than 5 cm but with a mitotic count of 6 (per 50 HPFs), and the other patient had a tumor that was larger in size (5 × 5 cm). EUS plays an important role in judging the origin of G-SMTs and can help to distinguish the tumor origin and growth pattern. Although a previous prospective study on the malignant risk of GIST found that tumor size and EUS characteristics cannot be used to predict the malignant risk of gastric GIST before surgery [40], our study showed that the ER failure rate of SMTs originating from the deep MP layer is much higher, indicating the important role of preoperative EUS. Regarding the tumor growth site, previous studies have shown that

the endoscope can easily reach the lower part of the stomach for surgery, so it seems easier to stop interoperation bleeding using this approach [45]. Studies have also shown that the upper gastric muscularis propria is thinner, so it is more likely to perforate [39]. There are abundant omental attachments on the greater and lesser curvature sides of the stomach, but there is no omental attachment on the anterior and posterior walls and fundus. We subdivided the patients into three groups according to the tumor location and the presence of omental attachments, but we did not find a significant difference among the three groups in our study. This finding is based on real data from our center, and we look forward to conducting more research in this area in the future.

Physician experience is a risk factor for ER failure. In this study, ESD/EFTR was performed by experienced or inexperienced endoscopists under the supervision of experts. Thus, the incidence of unfavorable ESD/EFTR results may vary. Moreover, experienced endoscopists tend to treat larger or more complicated cases. This reflects the actual clinical significance of our research, and the results of this study provide a reference of the risk factors that should be considered by clinicians managing these patients.

To minimize the effect of reverse causality, we repeated all analyses after excluding study cases in the previous 2 years, the association of irregular borders and endoscopists' experience with endoscopic resection failure changed in this model. In addition, irregular borders showed instability in the sensitivity analysis when excluding less experienced endoscopists. These findings suggest that irregular boundaries and endoscopists' experience outcomes were less stable, this result may be ascribed to reverse causality or be related to less ER failure cases. In both models above, tumors origin, tumor size and growth pattern were presented good stability.

There are several shortcomings of this study that should be mentioned: (1) this was a retrospective study, so the included subjects were limited to patients undergoing ER (ESD and EFTR) at our hospital. In addition, the sample range was relatively small. (2) The accuracy of EUS diagnosis is highly dependent on the endoscopist, and the difference between observers represents an important challenge to be addressed. (3) The consideration of the influencing factors of the results was limited, and not all possible influencing factors were included in the statistical analysis. Therefore, it is necessary to expand the sample size and try to consider and analyze the factors that may cause bias. (4) Finally, our institution is the Jiangsu Provincial Tertiary Endoscopy Center, so 97.2% of endoscopic operations are performed by experienced endoscopists. Therefore, it is necessary to consider the abovementioned risk factors with regard to the endoscopist level of experience.

Conclusions

In this study, patients with gastric submucosal tumors treated by gastroscopy at our hospital were used as the research subjects to analyze the risk factors for ER failure. The analysis of single factors and a combination of multiple factors showed that tumors originating from the deep MP layer, a maximum tumor diameter $\Phi > 3$ cm, an exophytic growth pattern, the experience level of the endoscopist, and irregular borders are independent risk factors for ER failure.

Declarations

Conflict of interest The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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