Review Article

Endoscopic resection of gastric gastrointestinal stromal tumors

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Abstract: Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal tumors in the gastrointestinal tract, and about 60% of them are found in the stomach. With the widespread application of endoscopy and endoscopic ultrasonography (EUS), more and more gastric GISTs are being found in an early stage (with a relative small diameter and no metastasis), giving the chance of complete resection. Endoscopic resection such as endoscopic band ligation (EBL), endoscopic submucosal dissection (ESD), endoscopic submucosal excavation (ESE), endoscopic full-thickness resection (EFTR) and submucosal tunneling endoscopic resection (STER), is a minimally invasive method compared with the conventional surgical approaches (open or laparoscopic), and has been demonstrated to be safe and effective for treating gastric GISTs. This review summarizes the recent advances on endoscopic resection of gastric GISTs, aiming to provide a rational management strategy for gastric GISTs.

Keywords: Endoscopic surgical procedures; gastric neoplasm; gastrointestinal stromal tumor (GIST)

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Introduction

Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal tumors in the gastrointestinal tract, and the estimated clinical incidence is 1 in 100,000 populations per year (1). GISTs can occur anywhere in the gastrointestinal tract, and in rare cases, in intra-abdominal sites (such as omentum, mesentery, and retroperitoneum), among which the stomach is the most common site (about 60%) (1). With the widespread use of endoscopy and endoscopic ultrasonography (EUS), more and more gastric GISTs are being found in an early stage, providing the chance of complete resection. Laparoscopic surgery (LAP) has been regarded as the standard methods for treatment of gastric GISTs <5 cm (2-4). Endoscopic resection takes advantages over LAP in reducing intraoperative blood loss, operating time and hospital stay without any compromise in success rate or increase in complications, and has been widely accepted as an alternative method for gastric GISTs originating from the MP layer (5-7). Available endoscopic methods include endoscopic band ligation (EBL), endoscopic submucosal dissection (ESD), endoscopic submucosal excavation (ESE), endoscopic full-thickness resection (EFTR), submucosal tunneling endoscopic resection (STER), and laparoscopic and endoscopic cooperative surgery (LECS) (8). This review summarizes recent advances on endoscopic resection of gastric GISTs, aiming to provide a rational management strategy for gastric GISTs.

Indications of endoscopic resection of gastric GISTs

Gastric submucosal tumors (SMTs) are found in 0.36% of middle-aged adults by health examination, and most of them are asymptomatic or have nonspecific symptoms (9). Once a gastric SMT is found, EUS is usually recommended

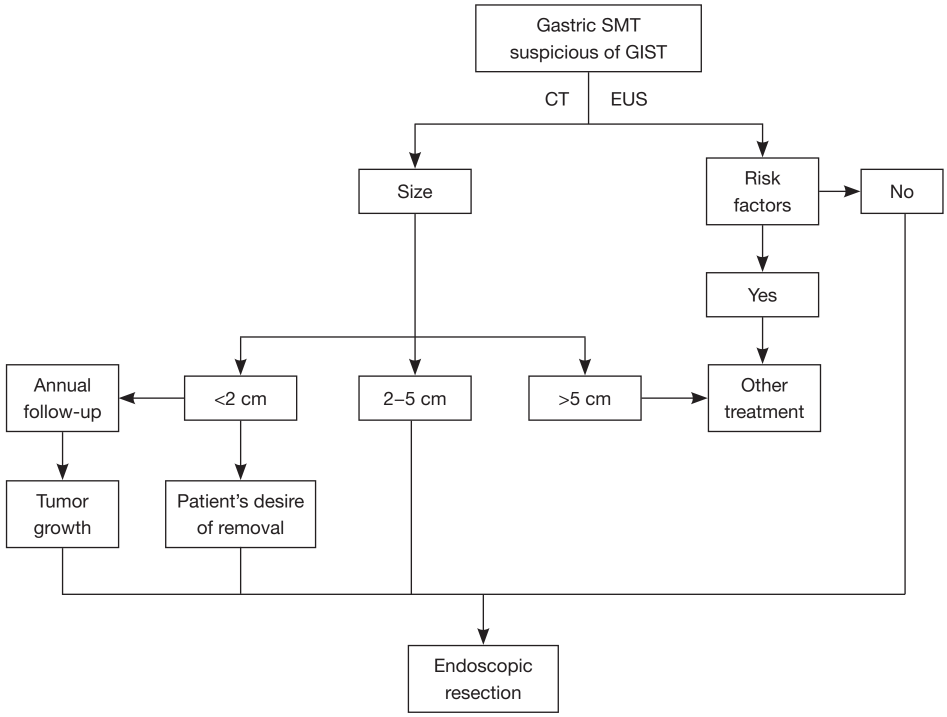

Figure 1 The patient selection diagram of endoscopic resection for gastric GISTs in our hospital. Risk factors: ulceration or erosion at the site of tumor location; EUS shows irregular border, internal heterogeneity include anechoic area (i.e., necrosis) and echogenic loci (i.e., bleeding), heterogeneous enhancement, regional lymph node swelling; CT show metastasis or invasion out of the gastrointestinal tract; a Zubrod-ECOG performance status ≥2; have severe cardiopulmonary disease or blood coagulation disorders. GIST, gastrointestinal stromal tumor; EUS, endoscopic ultrasonography; CT, computed tomography; SMT, submucosal tumor.

to further determine the characteristics of the SMT, such as the originating layer, echo, lymph node, which is helpful to differentiating GISTs from other mesenchymal tumors. Specific findings of GIST on EUS include: low echo, inhomogeneous, anechoic or high echo (when tumors are malignant), and it is usually located in the third or fourth layer, rarely the second layer (10). If an SMT is highly suggestive of a GIST and is considered resectable, preoperative biopsy is not necessary (11). Periodical surveillance is recommended for small (<2 cm) asymptomatic gastric GISTs. However, it involves issues related to the patient's compliance and stress, cost-effectiveness, and the risk associated with repeated endoscopic procedures and delayed diagnosis of malignancy (12,13). Moreover, it is believed that small gastric GISTs also have malignant potential and that the size of small gastric GISTs could increase significantly during follow-up (13,14). Therefore, some researchers suggested that once a gastric GIST was suspected, it should be resected by surgical or endoscopic approaches (13,15), although the NCCN guideline did not recommend immediate resection for GISTs <2 cm (2). *Figure 1* shows the patient selection diagram of endoscopic resection for gastric GISTs in our hospital.

Endoscopic methods for gastric GIST

EBL

EBL was first reported for treating esophageal varices (16), and was then applied to the treatment of gastrointestinal superficial lesions (17). Sun *et al.* (18) firstly reported the feasibility and safety of EBL in the treatment of gastric GISTs, and complete resection was achieved in 96.6% (28/29) of the cases, with a low complication rate (3.4%, 1/29) and recurrence rate (3.4%, 1/29). The standard procedure of EBL is as follows: aspirating the tumor into a transparent cap, releasing the band, cutting the overlying mucosal and submucosal layer and then dissecting the

Table 1 Studies about endoscopic resection for gastric GISTs

Ref.	N	Method	Mean tumor diameter [range] (mm)	Mean operation time (min)	Complete resection rate (%)	Complication (%)	Recurrence (%)
Sun *et al.* (18)	29	EBL	9.2 [7–12]	–	96.6	1 bleeding	3.4
Nan *et al.* (19)	24	EBL	8 [7–12]	–	100	0	0
Huang *et al.* (21)	38	EBL	<12	–	100	3 perforation	–
Nan *et al.* (20)	177	EBL	8 [5–12]	–	100	2 perforation	–
An *et al.* (22)	168	ESD	15 [5–60]	46.5 [33–181]	100	2 bleeding, 71 gastric wall defect	0
He *et al.* (23)	25/31[†]	ESD	27 [20–50]	70.16 [40–105]	100	3 bleeding, 6 perforation	0
Zhang *et al.* (24)	69	ESE	18.7 [7–30]	41.07±10.79	100	6 bleeding, 23 perforation, 5 surgery-related complication	0
Huang *et al.* (21)	18	ESE	>15	–	100	0	–
Wang *et al.* (25)	86	ESE	–	–	100	5 bleeding, 9 perforation	5.8
Shi *et al.* (26)	43/60[‡]	ESE	1.4 [5–50]	38	100	–	–
Wang *et al.* (27)	30	ESE	22 [10–35]	50±5 [20–120]	100	6 perforation	0
Shi *et al.* (28)	68	EFTR	26	41	100	1 Mallory-Weiss syndrome, 1 delayed bleeding	0
Mori *et al.* (29)	16	EFTR	28.3	271	100	0	0
Huang *et al.* (21)	13	EFTR	>20	–	100	0	–
Lu *et al.* (30)	36/47[§]	STER	14 [5–50]	79.3 [45–150]	100	3 peumoperitoneum	0
Li *et al.* (31)	11/32[§]	STER	23 [10–50]	51.8 [25–125]	100	Intraoperative: 1 bleeding, 6 peumoperitoneum; postoperative: 3 pneumothorax, 3 pleural effusion, 1 subphrenic infection	0
Mao *et al.* (32)	10/56[§]	STER	18 [10–32]	41.5 [20–65]	100	9 gas-related complications with or without pleural effusion	0
Kikuchi *et al.* (33)	10	LECS	24.1±7.6	253±45	100	1 intra-abdominal abscess	0
Qiu *et al.* (34)	69	LECS	28±16	86.1	–	1 leakage, 1 bleeding	0
Hiki *et al.* (35)	10	LECS	46±3	169±17	100	0	–

[†], 25 of the 31 GISTs were located in the stomach; [‡], 43 of the 60 GISTs were located in the stomach; [§], n/m, these 3 studies are about STER for gastric submucosal tumors, n of the m submucosal tumors are gastric GISTs. GISTs, gastrointestinal stromal tumors; EBL, endoscopic band ligation; ESD, endoscopic submucosal dissection; ESE, endoscopic submucosal excavation; EFTR, endoscopic full-thickness resection; STER, submucosal tunneling endoscopic resection; LECS, laparoscopic and endoscopic cooperative surgery.

tumor. EUS is usually used to confirm whether the mass is completely confined within the band, and hemoclips are placed around the band to reduce the tension and potential perforation. Several clinical studies have demonstrated the safety and efficacy of EBL for gastric GISTs, with favorable complete rate, low complication and recurrence rate (19,20) (*Table 1*). The most common complications reported are perforation and bleeding (18-20,36). In addition, Meng *et al.* (5) demonstrated that EBL could reduce operation time, estimated blood loss, complications, hospital stay and cost, compared with ESD and LAP. The major disadvantage of EBL is the restriction of maximal resectable size (≤12 mm) due to the size of the transparent cap. And EBL is feasible only for GISTs originating from superficial muscularis propria layer. EBL is now less used and mostly be replaced by other endoscopic methods.

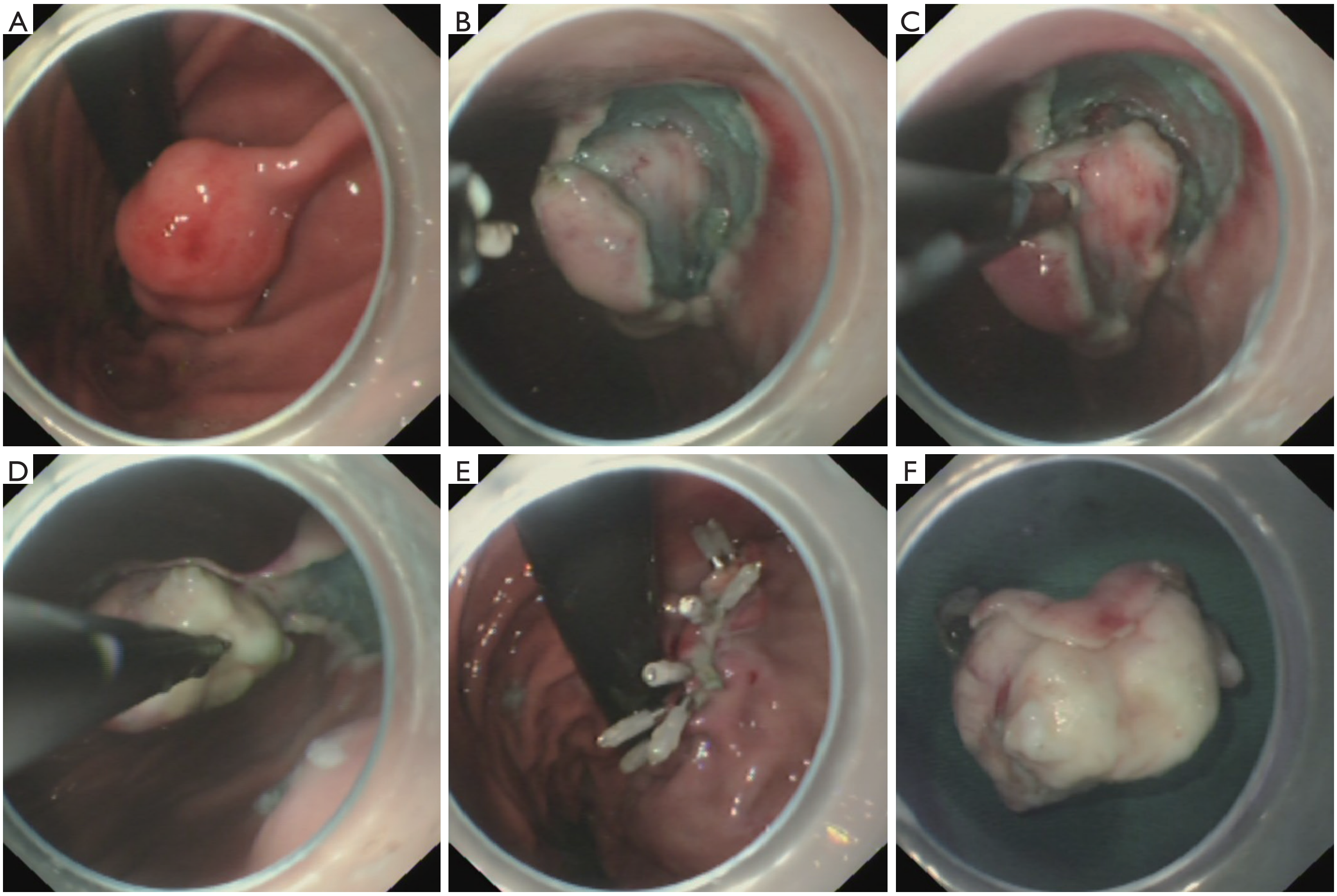

Figure 2 Case illustration of endoscopic submucosal dissection. (A) We could see a submucosal tumor in the gastric fundus; (B) after making dots and submucosal injection, we precut the mucosal and submucosal layer using a dual knife, and the submucosal tumor is shown; (C,D) dissect the tumor with a dual knife; (E) close the wound with several clips; (F) the resected tumor.

ESD

ESD was firstly used to treat early stage gastric cancer (37), and was then applied to the treatment of gastric SMTs, including gastric GISTs (38,39). The standard procedure of ESD is as follows: making marking dots around the lesion, submucosal injection, precutting the mucosal and submucosal layer and then dissecting the tumor (*Figure 2*). Compared with EBL, ESD enables a larger resectable size and provides a higher *en bloc* resection rate. Although many clinical studies concerning the treatment of ESD for gastric SMTs (GISTs included) have been reported [see in detail in review (40)], only two studies have been published regarding ESD as a treatment for pure gastric GISTs (*Table 1*), and both of their results were exciting. Moreover, Meng *et al.* (41) demonstrated that the efficacy of ESD and LAP for treating small gastric GISTs was comparable, but ESD could reduce the operation time, estimated blood loss and hospital stay. Perforation and bleeding are the major complications associated with gastric ESD, whose incidence have been reported to range from 0% to 8.2% and 0% to 15.6%, and most of them can be successfully managed by appropriate endoscopic interventions [see in detail in review (42,43)]. Other rare but serious complications include aspiration pneumonia, stenosis, venous thromboembolism, and air embolism (44-47). Endoscopists should be aware of these complications and their associated risk factors (44-47), so as to prevent their occurrence and reduce the harm. And to achieve an *en bloc* resection, ESD is only recommended for SMTs originating from the superficial MP layer.

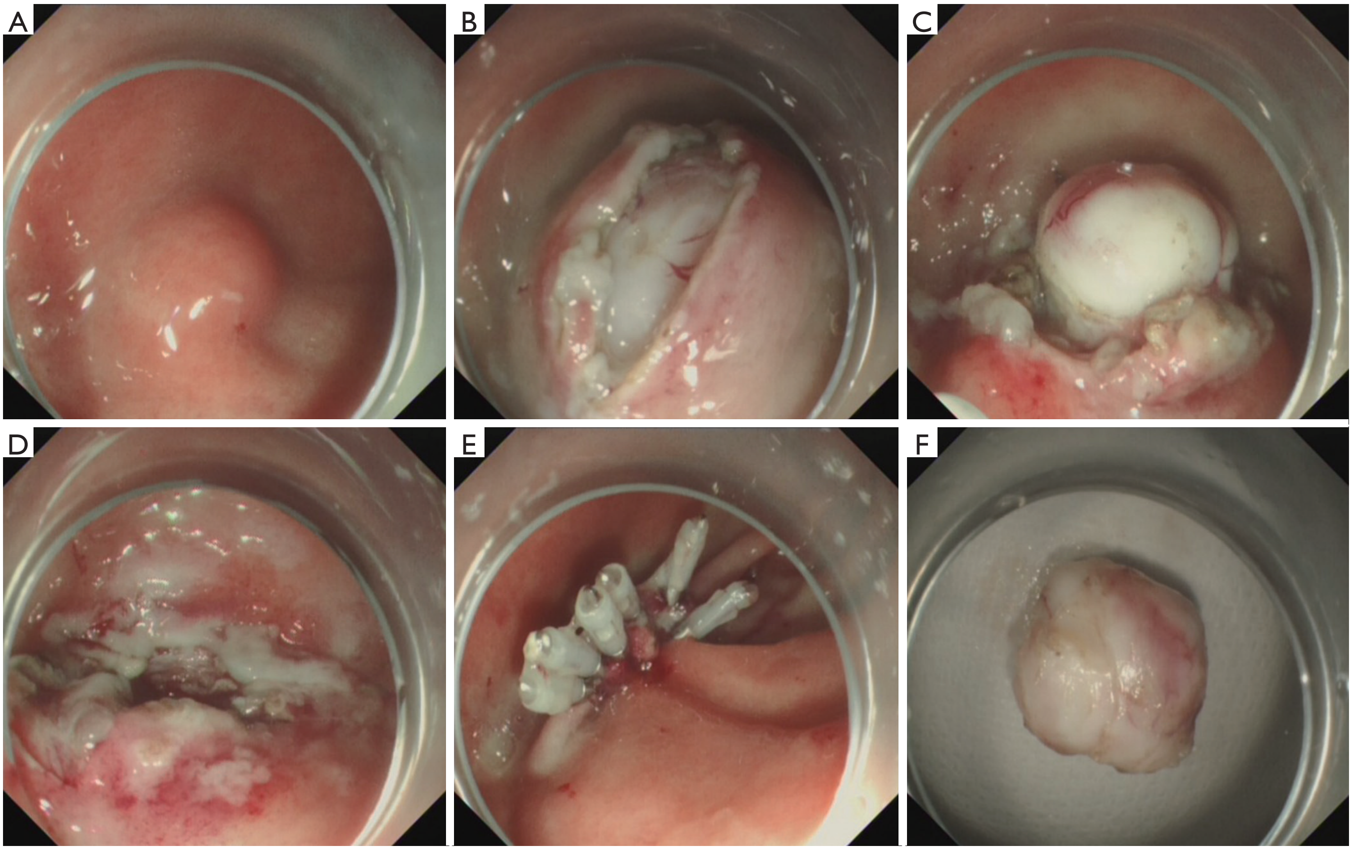

Figure 3 Case illustration of endoscopic submucosal excavation. (A) We could see a submucosal tumor in the gastric corpus; (B) after making dots and submucosal injection, we precut the mucosal and submucosal layer covering the submucosal tumor to expose the tumor; (C) excavate the tumor from the muscularis propria layer; (D) the wound surface after tumor removal; (E) close the wound with several clips; (F) the resected tumor.

ESE

Although ESD is effective for treating gastric GISTs, the en bloc resection rate sometimes is not that satisfactory, especially for those originating from deep MP layer. ESE, allowing deep excavation, is a better choice. ESE was first reported by Jeong *et al.* (48) for treating gastric SMTs (GISTs included) originating form the MP layer, with a high complete resection rate and acceptable complication rate. The standard procedure of ESE is as follows: making marking dots around the lesion, submucosal injection, precutting the mucosal and submucosal layer and excavating the tumor (*Figure 3*). The major difference between ESD and ESE procedure is the depth of endoscopic resection. As deep excavation was necessary during ESE, an insulated-tip knife is usually recommended during excavation to avoid or reduce unintentional injury, while in the ESD procedure, the dissection could achieved by other endoscopic knives such as dual knife, hook knife, etc. Several studies have demonstrated the safety and efficacy of ESE for gastric GISTs, with favorable complete rate and low recurrence rate (24,26,27) (*Table 1*). The most common complication reported is perforation, whose incidence was up to 33.3%. However, most of them could be successfully managed by endoscopy, only few needed surgical intervention. Other reported complications include bleeding, surgery-related complications, bacteremia (21,24,26,27,48,49). CO_2 is recommended during the procedure, as it can reduce the pain score and increase the visual analog scale score, compared with air insufflation (26).

EFTR

EFTR was firstly reported by Suzuki and Ikeda for treating

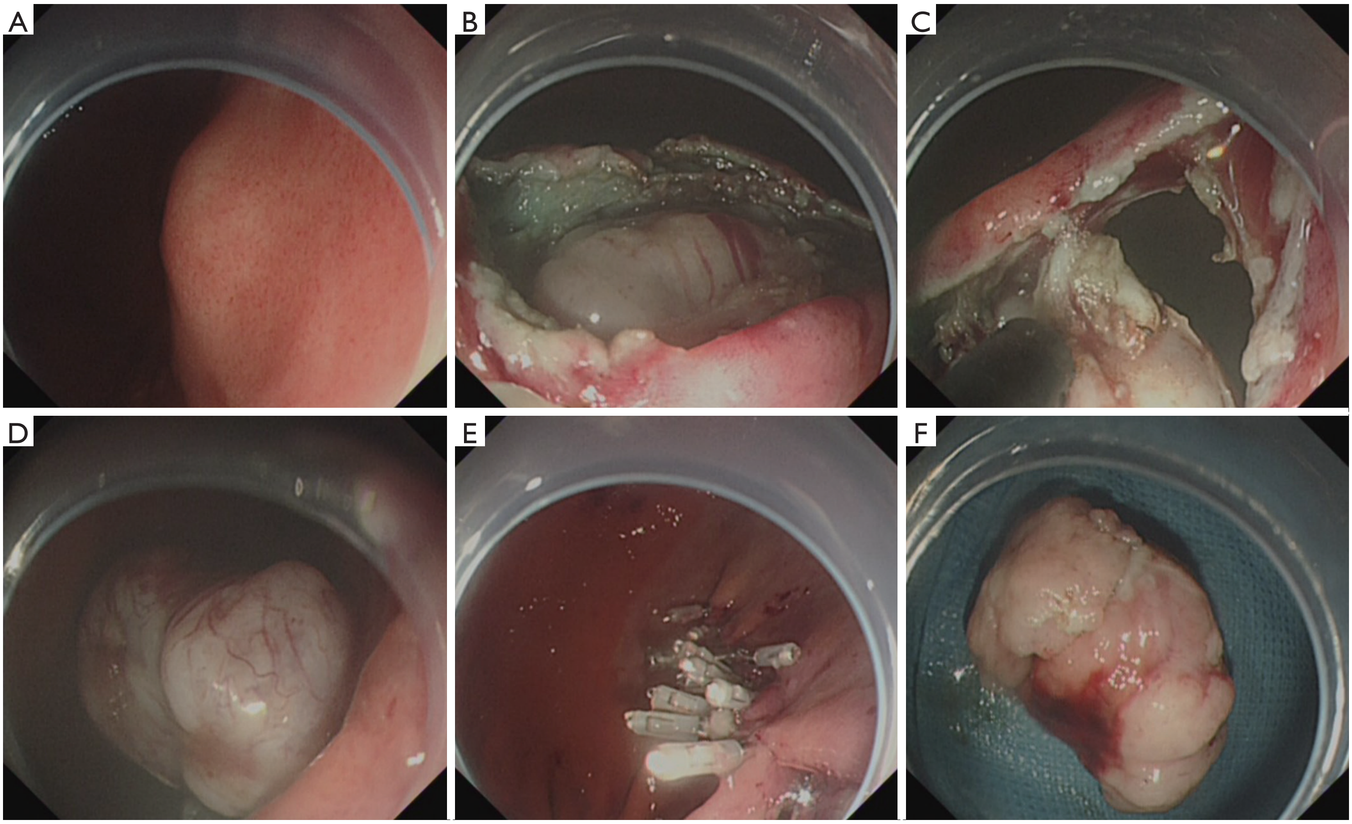

Figure 4 Case illustration of endoscopic full-thickness resection. (A) We could see a submucosal tumor in the gastric corpus; (B) after submucosal injection, we precut and remove the mucosal and submucosal layer to expose the tumor; (C,D) endoscopic full-thickness resection of the tumor, we could see the abdominal cavity through the "active perforation"; (E) close the wound with several clips; (F) the resected tumor.

two rectal carcinoids and one duodenal carcinoid using the snaring technique (50), and then Ikeda *et al.* reported EFTR using the ESD technique on a porcine stomach (51). Wang *et al.* (52) firstly introduced EFTR into clinical practice for treating gastric GISTs. The standard procedure of EFTR is as follows: submucosal injection, precutting the mucosal and submucosal layer around the lesion, circumferential incision as deep as the MP layer around the lesion, incision into the serosal layer around the lesion, full-thickness resection of the tumor including the serosal layer and closing the gastric-wall defect (*Figure 4*). Although many clinical studies concerning EFTR for gastric SMTs have been published, only three studies are available about EFTR for pure gastric GISTs (21,28,29), and the clinical outcomes were promising (*Table 1*). In EFTR, perforation is not considered as a complication. Reported complications include bleeding, localized peritonitis, abdominal distention, etc., and the overall complication rates were very low [in detail in review (53,54)]. Furthermore, Wang *et al.* (55) found that the safety and efficacy of EFTR and LAP for small gastric GIST is comparable, however, EFTR could reduce the procedure time, intraoperative bleeding volume and hospital stay. Besides, 12 of the 33 cases needed intraoperative endoscopy to precise identify the GISTs in the LAP group.

STER

STER was initially used as a therapeutic technique for treating esophageal and cardia SMTs (56-59). The standard procedure is as follows: submucosal injection, creating tunnel entry, submucosal tunnel creation, finding and dissecting the SMT, and then closing the tunnel entry (*Figure 5*). Compared with other endoscopic methods, STER possesses multiple advantages including the maintenance of mucosal integrity, the facilitation of an increased healing rate and a decreased risk of pleural/

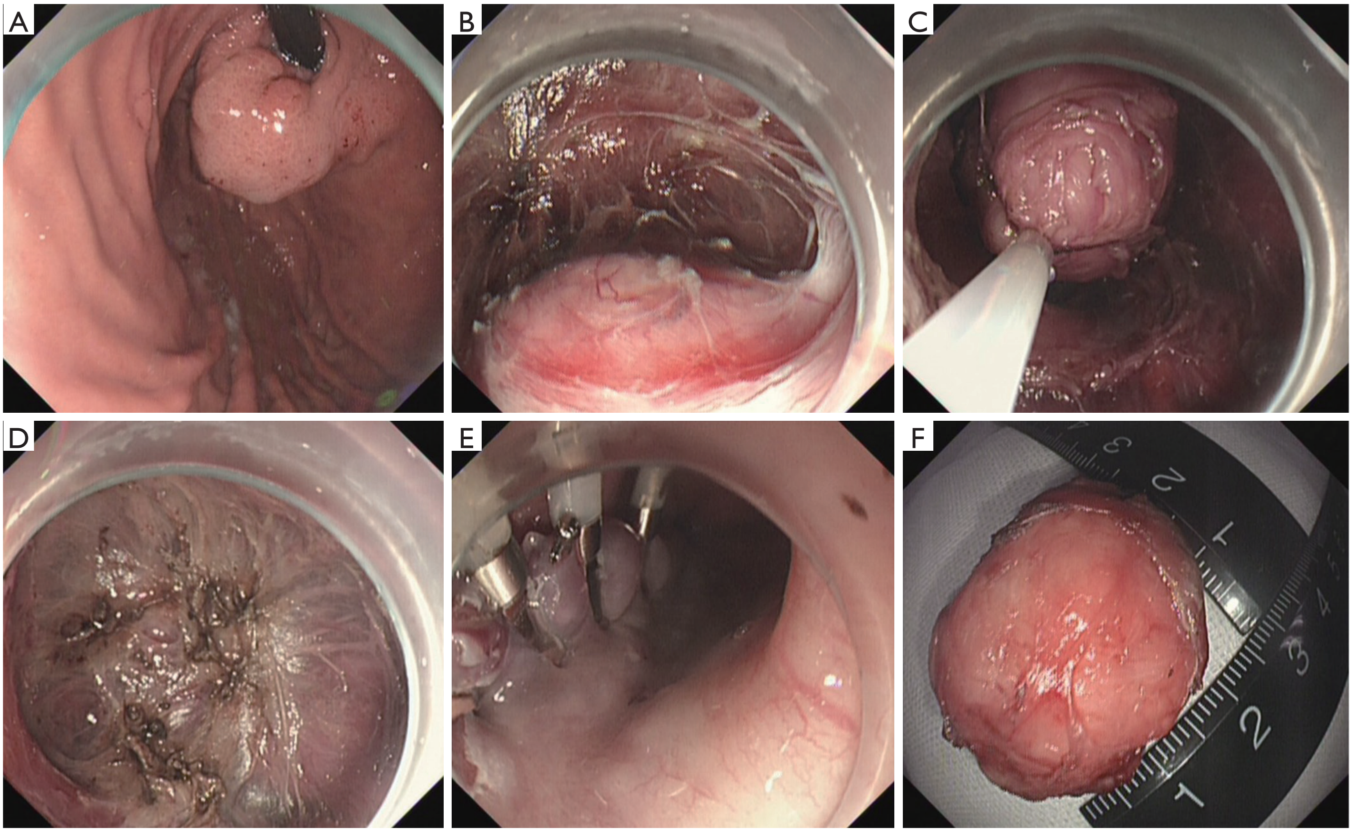

Figure 5 Case illustration of submucosal tunneling endoscopic resection. (A) We could see a submucosal tumor in the gastric fundus; (B) after submucosal injection, a longitudinal mucosal incision was made 3 cm above the tumor, and a submucosal tunnel was created between the submucosal and muscularis propria layer, and then the submucosal tumor was visible; (C) carefully dissected the tumor from the muscularis propria layer and remove the tumor; (D) the wound surface after tumor removal; (E) close the tunnel entry with several clips; (F) the resected tumor.

abdominal infection (60-62). Several studies have demonstrated the safety and efficacy of STER for treating gastric SMTs, half of whom were gastric GISTs (30-32). Zhang *et al.* (63) found that compared with endoscopic nontunneling methods (ESD and EFR), STER has no distinct advantages in treating relatively small gastric SMTs, but Tan *et al.* (64) found that the safety and efficacy between STER and EFTR were comparable, but patients who received EFTR needed more clips to close the gastric wall defect. Common complications of STER include gas-related complications, bleeding, pleural effusion, mucosal injury, etc. Although the overall incidence of complications is relatively high, only a small part of them need therapeutic intervention (59,65), suggesting STER is a safe and effective method.

LECS

All the above endoscopic methods have limitations in terms of rumor size and location, thus the concept of LECS was devised, consisting of endoscopic surgery in the form of endoscopic mucosal incision and LAP (35). In this advanced technique, incision lines are confirmed endoscopically and accurately determined by application of an endoscopic mucosal/submucosal incision technique, while the seromuscular layer is incised laparoscopically and the incision line is closed using a laparoscopic stapling device, resulting in minimal dissection of the normal gastric wall with minimal gastric transformation. Currently, LECS has been recommended by NCCN as a treatment for gastric GIST less than 50 mm in diameter regardless of the tumor

Table 2 Comparison of different endoscopic methods for gastric GISTs

Ref.	Method	N	Mean tumor diameter (mm)	Mean operation time (min)	*En bloc* resection rate (%)	Complication (%)	Follow-up time (months)	Recurrence (%)
Meng *et al.* (5)	EBL *vs.* ESD	72 *vs.* 27	10.68 *vs.* 11.78	17.11 *vs.* 65.26	–	1.39 *vs.* 18.52	6 *vs.* 7	15 *vs.* 9.1
Tan *et al.* (64)	STER *vs.* EFTR	20 *vs.* 32	17.8 *vs.* 15.4	74.9 *vs.* 69.1	95 *vs.* 96.9	5 *vs.* 15.6	10.9 *vs.* 23.8	0 *vs.* 0
Zhang *et al.* (63)	Nontunneling *vs.* STER	78 *vs.* 19	15 *vs.* 20	50 *vs.* 75	95.9 *vs.* 94.1	26.9 *vs.* 36.8	–	0 *vs.* 0
Balde *et al.* (66)	LECS *vs.* ESD	30 *vs.* 30	15 *vs.* 15	96.5 *vs.* 41.5	100 *vs.* 100	3.3 *vs.* 26.7	–	0 *vs.* 14.3
Ojima *et al.* (67)	LECS *vs.* EIGS	21 *vs.* 26	25 *vs.* 23	139 *vs.* 108	100 *vs.* 100	4.8 *vs.* 40	21 *vs.* 61	4.8 *vs.* 4

GISTs, gastrointestinal stromal tumors; EBL, endoscopic band ligation; ESD, endoscopic submucosal dissection; EFTR, endoscopic full-thickness resection; STER, submucosal tunneling endoscopic resection; LECS, laparoscopic and endoscopic cooperative surgery; EIGS, endoscopic intragastric surgery.

location (2). Since it's first reported by Hiki *et al.* (35), two other studies have explored the efficacy of LECS for gastric GISTs and have shown exciting results (33,34). In addition, Balde *et al.* (66) found that although ESD had a shorter operation time, the rate of intraoperative complications was lower in the LECS group. Ojima *et al.* (67) found that compared with LECS, endoscopic intragastric surgery (EIGS) had a higher perioperative complications rate and a longer time to resumption of first oral intake.

Postoperative management

All the patients are kept nil per os (NPO) for at least 72 h, a liquid diet for 5 days, and returned gradually to a normal diet within 2 weeks. And intravenous proton pump inhibitor (PPI) and antibiotics were recommended for at least 3 days. For patients with GISTs located in the gastric fundus, they are asked to keep a semireclining position for 3 days. A contrast roentgenography is performed on postoperative day 3 to check for any occurrence of leakage. Ultrasound was applied to check the presence of any abdominal or pelvic dropsy.

The resected specimens are fixed, embedded with paraffin and then sectioned. Hematoxylin and eosin and immunohistochemical staining (CD117, CD34, Dog-1, Ki67, SMA, etc.) are carried out to determine whether the SMT is a GIST or not. If the SMT is highly suspected of a GIST but all the markers above are negative, KIT and/or PDGFRA mutation should be detected (68). A risk category should obtained based on the tumor size, mitotic index and primary tumor site using the modified NIH classification system (69), classifying them as very low risk, low risk, intermediate risk and high risk, which is helpful to predict recurrence. For those patients classified as intermediate or high risk, additional surgery and/or adjuvant treatment (imatinib, etc.) are recommended.

Postoperative follow-up is necessary for GISTs patients who received endoscopic resection, and the surveillance interval varies according to the risk classification. For patients with high or intermediate risk, abdominal and pelvic CT or EUS every 3–4 months is recommended in the first 3 years after endoscopic treatment, and then every 6 months until 5 years after treatment and then annually thereafter. For those with very low or low risk, CT and/or EUS are recommended every 6 months in the first 5 years (68,70). Surveillance endoscopy is recommended to be performed at 3 months, and 12 months after treatment to observe healing of the wound and to check for any residual tumor.

Conclusions and perspectives

Unpredictable malignant potential and rare lymph node metastasis provide the theoretical basis of minimally invasive treatment of gastric GISTs. Currently, many studies concerning endoscopic resection for gastric GISTs have been published, and the primary results were exciting (*Table 1*). However, the follow-up of these studies were relative short (usually <2 years), thus warranting a long-term follow-up. What's more, few studies that focused on the comparison among different endoscopic methods or between endoscopic and surgical methods have been published (*Tables 2,3*). Thus more evidence is required to recommend endoscopic resection as the first-line treatment

Table 3 Comparison between endoscopic and surgical methods for gastric GISTs

Ref.	Method	N	Mean tumor diameter (mm)	Mean operation time (min)	Complete resection rate (%)	Complication (%)	Follow-up time (months)	Recurrence (%)
Meng *et al.* (5)	EBL *vs.* LAP	72 *vs.* 48	10.68 *vs.* 12.02	17.11 *vs.* 90.81	–	1.39 *vs.* 4.17	6 *vs.* 6	15.00 *vs.* 11.76
Meng *et al.* (41)	ESD *vs.* LAP	75 *vs.* 51	14.4 *vs.* 14.6	63.59 *vs.* 79.12	–	2.67 *vs.* 1.96	40.1 *vs.* 40.9	2.67 *vs.* 1.96
Wang *et al.* (55)	EFTR *vs.* LAP	35 *vs.* 33	13 *vs.* 16	91 *vs.* 155	100 *vs.* 100	11.4 *vs.* 13.3	–	0 *vs.* 0
Wu *et al.* (71)	EFTR *vs.* LAP	50 *vs.* 42	–	85 *vs.* 88	100.0 *vs.* 92.9	0 *vs.* 4.8	–	0 *vs.* 0
Huang *et al.* (72)	EFTR *vs.* LAP	32 *vs.* 30	–	78.5 *vs.* 80.9	100.0 *vs.* 93.3	0 *vs.* 3.3	–	0 *vs.* 0
Wang *et al.* (52)	EFTR *vs.* LAP	66 *vs.* 43	15 *vs.* 11	53.6 *vs.* 139	98.4 *vs.* 100.0	24.2 *vs.* 14.0	–	0 *vs.* 0
Dong *et al.* (73)	EFTR *vs.* MLIGS	10 *vs.* 8	16.5 *vs.* 27.5	120 *vs.* 85	100 *vs.* 100	10 *vs.* 0	–	0 *vs.* 0

GISTs, gastrointestinal stromal tumors; EBL, endoscopic band ligation; ESD, endoscopic submucosal dissection; EFTR, endoscopic full-thickness resection; LAP, laparoscopic surgery; MLIGS, modified laparoscopic intragastric surgery.

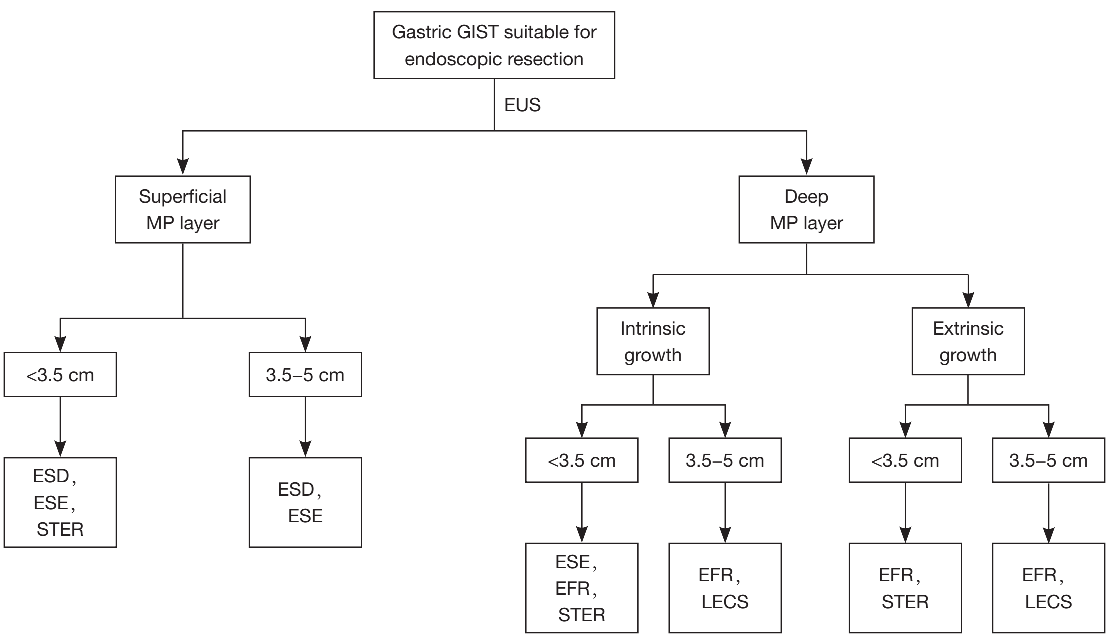

Figure 6 Algorithm on endoscopic management of gastric GISTs in our hospital. GIST, gastrointestinal stromal tumor; EUS, endoscopic ultrasonography; MP, muscularis propria; ESD, endoscopic submucosal dissection; ESE, endoscopic submucosal excavation; STER, submucosal tunneling endoscopic resection; EFR, endoscopic full-thickness resection; LECS, laparoscopic and endoscopic cooperative surgery.

of gastric GISTs. In our hospital, we use an algorithm as proposed in *Figure 6*.

Furthermore, to expand the role of endoscopy on the treatment of gastric GISTs, several technical problems need to be resolved. Firstly, we need to find ways to reduce complications of endoscopic resection, especially perforation. Although several devices such as over-the-scope clip have been proposed [see in review (74,75)], most of them are not suitable for large GISTs, thus warranting the development of new devices. Secondly, there is a possibility of pseudocapsule injury during endoscopic resection of a gastric GIST, providing the risk of peritoneal seeding. Thus a more secure endoscopic method is needed, and it should be performed by a well-trained endoscopist. Recently, novel hybrid techniques, such as combination of laparoscopic and endoscopic approaches to neoplasia with non exposure technique (CLEANNET) (76) and non-exposed endoscopic wall-inversion surgery (NEWS) (77,78), could avoid exposing malignant SETs to the peritoneal cavity. In conclusion, technical modifications and improvements are required to define the role of endoscopy for treating gastric GISTs.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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