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ORIGINAL ARTICLE

Laparoscopy-assisted endoscopic full-thickness resection for gastric subepithelial tumors originated from the muscularis propria layer: a pilot study with literature review

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ABSTRACT

Objective: Laparoscopy-assisted endoscopic full-thickness resection (LAEFTR) has been suggested as an alternative to laparoscopic wedge resection in the treatment of gastric subepithelial tumors (SETs). It is expected to minimize the resection of the tissue surrounding the tumors and maintain the function of the remnant stomach. Here, we performed a prospective pilot study to evaluate the efficacy of laparoscopy-assisted endoscopic full-thickness resection (LAEFTR) for patients with gastric SETs.

Material and methods: We enrolled twelve patients who were diagnosed with gastric SETs with an intraluminal growth pattern or which is located in the gastric antrum between October 2011 and September 2013. LAEFTR was performed endoscopically using an endoscopic knife to make an incision half way around the tumor circumference and a laparoscopic resection around the remaining tumor circumference, followed by its laparoscopic removal. The feasibility, safety, and effectiveness of LAEFTR for gastric SETs were evaluated.

Results: The median size of the tumors in twelve patients was 22 mm (21–33). Of the 12 patients, 8 received LAEFTR, while the others underwent conventional laparoscopic wedge resection, since their tumor outlines were clearly visible in laparoscopic view. In 8 patients who underwent LAEFTR, the mean total operation time (endoscopic procedure time/laparoscopic procedure time) were 117 (37/41) min. The tumors were completely resected with clear margin, and there was no perioperative and postoperative complications.

Conclusions: LAEFTR currently seems to be the ideal treatment modality of intraluminal gastric SETs where their resection margins are difficult to define under laparoscopic guidance alone.

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Endoscopy; gastrointestinal; laparoscopy; stomach neoplasms; subepithelial tumors

Introduction

Gastric subepithelial tumor (SET)s are found more frequently in East Asian countries like Korea and Japan, ever since upper gastrointestinal endoscopy or gastrography has been routinely included in the national cancer screening program in these countries. Therefore, recently detected gastric SETs have been smaller in size than in the past. Gastrointestinal stromal tumor (GIST) is one of the most common gastric SETs, and some of them exert malignant behavior, in spite of its small size. According to current guidelines for management of SETs, GISTs greater than 2 cm should be completely resected.[1] Therefore, the principle of resection is to remove tumors with the tumor-free margin macroscopically and without the tumor rupture microscopically.

Until now, laparoscopic wedge resection (LWR) has been recommended as a suitable treatment of choice for the gastric SETs originated from the muscularis propria (MP) layer.[2,3] However, one major limitation for this LWR procedure is that some small intraluminal gastric SETs are not easily detected. In such cases, it may be difficult to decide a suitable resection margin under laparoscopic guidance alone. Therefore, improper resection with unsuitable margin for small intraluminal SETs, especially around the esophago-gastric junction or the pyloric ring, may lead to an impairment of gastric function. Recently, in a few case series, endoscopic resection was attempted on selected SETs originating in the MP layer to overcome these limitations.[4–10] However, insufficient safety margin or even tumor seeding should be taken into account in an oncological view, and the dissection for obtaining sufficient safety margin can cause procedure-related perforation of the stomach wall. Therefore, a novel treatment modality of such intraluminal SETs is required.

Recently, hybrid resection, which is an endoscopic full-thickness resection simultaneously with laparoscopic surgery, has been suggested as an alternative treatment option to overcome the limitations generally found when endoscopic resection [4–10] or LWR [11–13] are done separately. Through endoscopic/laparoscopic examination, location and the extent of the tumor can be properly identified and

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resection along the boundary of the tumor is more accurate leaving a suitable resection margin than laparoscopic resection alone, even in tumors that cannot be easily removed using the LWR technique. Therefore, we speculate that hybrid resection conjoining both of endoscopic and laparoscopic procedures can ultimately be the ideal modality for treatment of small gastric SETs; especially located in the antrum or cardia, or having an intraluminal growth pattern.

Here, we conducted this pilot study with the aim to describe the technical details of laparoscopy-assisted endoscopic full-thickness resection (LAEFTR) and assess the feasibility and the surgical outcome in patients with gastric SETs originating in the MP layer.

Methods

Study design and study population

The patients, who presented with gastric SETs and were over 20 years old, were enrolled consecutively between October 2011 and September 2013. The inclusion criteria for gastric SET were as follows: (1) located in the MP layer confirmed using endoscopic ultrasonography (EUS); (2) showing an intraluminal growth pattern via either computer tomography or EUS, therefore expected not to be detectable under laparoscopic view; (3) without a histological diagnosis before the operation, but with a diameter between 2 cm and 4 cm in size; and (4) a confirmed pathological diagnosis of GIST after EUS-guided fine needle aspiration.

We excluded patients from our study if patients fell under the following: (1) the malignant potential – EUS findings such as cystic spaces, heterogenous echogenicity, or irregular margin, endoscopic findings such as ulceration or bleeding, or computer tomography findings such as necrosis, bleeding, irregular margin, or adjacent lymphadenopathy; (2) under 20 years of age; (3) American Society of Anesthesiologists' classification of IV or V; (4) past history of surgical gastrectomy; (5) pregnancy; or (6) coagulation disorder. Written informed consent for inclusion in the study was obtained from all the patients. The study protocol was approved by the institutional review board of Ajou university hospital.

Laparoscopic preparation

Patients fasted from midnight the day before surgery. Nasogastric tube was not inserted, but prophylactic antibiotics were given intravenously during perioperative period. Intermittent pneumatic compression device was applied to prevent perioperative thrombosis in the deep veins. After induction of general anesthesia, patients were placed in the reverse Trendelenberg position.

A single surgeon (H Hur), with an experience of over 100 laparoscopic surgeries for gastric neoplasm performed all of the laparoscopic procedures. A 10-mm trocar was inserted through the infraumbilical area using the Hasson open technique. And then, a forward-viewing laparoscope was introduced through the infraumbilical trocar, following the insufflation of carbon dioxide into the peritoneal cavity at a pressure of 10 mmHg. Two or three additional trocars were inserted into the peritoneal cavity, where their insertion location was decided based on the individual tumor characteristics. Greater or lesser omentum attached to the stomach was dissected using ultrasonic scissors (Harmonic Scalpel, Ethicon Endo-Surgery, New Brunswick, NJ), if the gastric SET was located in the posterior wall or the lesser curvature of the stomach. When the liver blocked the laparoscopic view, the liver was retracted to avoid the concealment of the operative field according to previously reported method to avoid the disturbance of surgical view.[14] When the location of the gastric SET was identified via the laparoscopic view, the laparoscopic resection was done without the aid of gastroscopy. If it was not, an endoscopic procedure was initiated after a laparoscopic bowel grasper was clamped onto the proximal jejunum to prevent the leakage of inflated intragastric air into the small bowel during the endoscopic procedure, which aids in making a transgastric endoscopic procedure easier.

Endoscopic procedures

All of the endoscopic procedures were performed by one expert endoscopist (SG Lim) with the experience of over five-hundred endoscopic submucosal dissection (ESD) cases of gastric neoplasm. A forward-viewing gastroscope (GIF-Q260J; Olympus Medical Systems Corp., Tokyo, Japan) was advanced into the stomach. After searching for then confirming the target lesion, standardized ESDs were performed to the process of submucosal incision around the tumors. Then, a puncture through the MP layer was made with the flex knife and a full-thickness incision was performed at least around two-thirds or half of the tumor circumference using the IT knife, with the help of straining the gastric wall near the tumor using laparoscopic grasping forceps making it easier to incise (Figure 1). If the endoscopic circumferential incision cannot be completed due to poor visibility, the lesion was everted into the peritoneal space using grasping forceps inserted through one of the trocars. The incision of the remaining circumference was performed using a Harmonic Scalpel for complete resection under a laparoscopic view. The resected specimen was retrieved through an infraumbilical trocar site using a specimen containment device (Endopouch Retriever; Ethicon Endo-Surgery) (Figure 2). After resection, the incised opening of the gastric wall was sutured in an interrupted double layer fashion with a #3-0 Vicryl suture thread using a laparoscopic suturing device (Ethicon Inc., Somerville, NJ) in a perpendicular direction to food passage to avoid narrowing of the gastric lumen (Figure 3). After suturing, a gastroscopy was re-advanced into the stomach to identify whether bleeding or luminal narrowing at the resected site occurred or not. Finally, surgical drain tubes were inserted around the operation field.

Postoperative care and follow-up

Routinely, patients maintained their fasting state for about 24 h after the surgery. They were only allowed to drink water

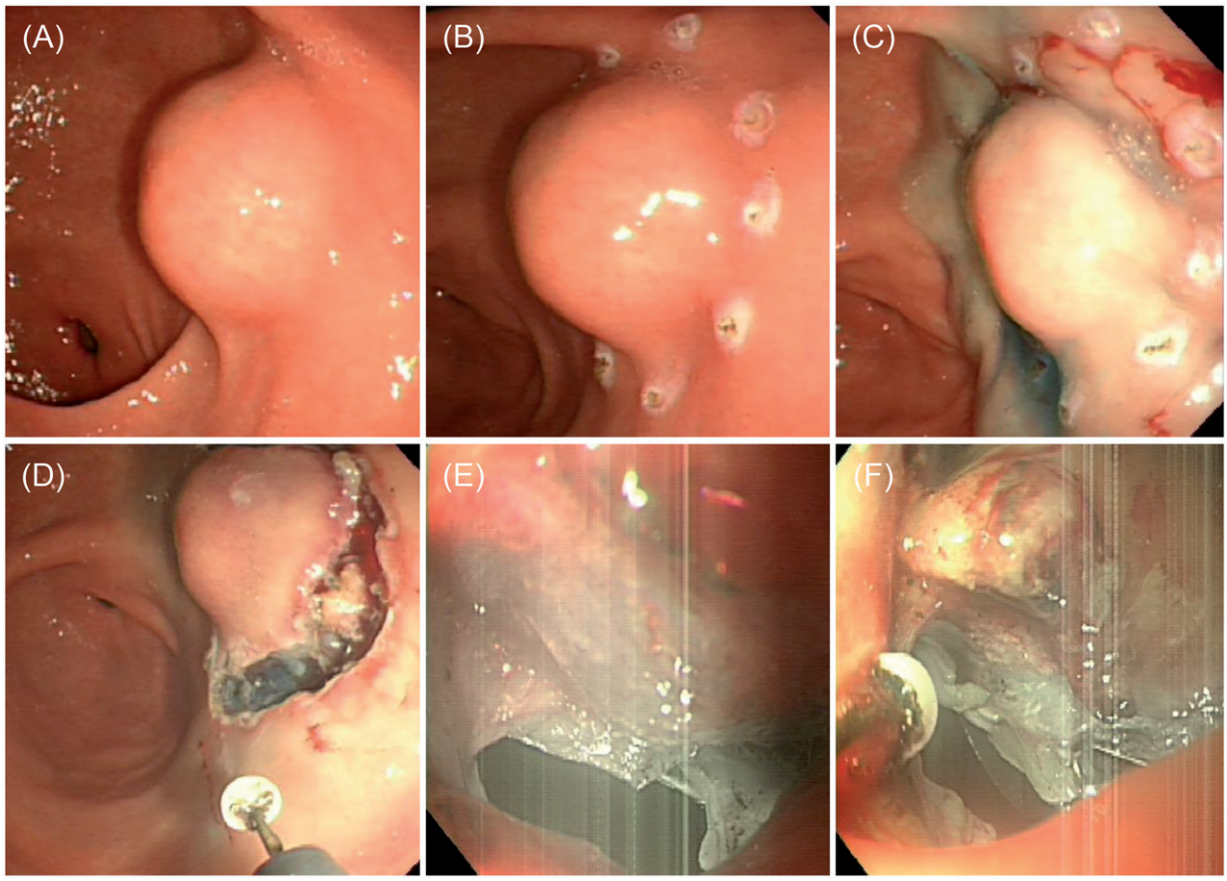

Figure 1. The endoscopic view of hybrid resection of a gastric subepithelial tumor. (A) The gastric subepithelial tumor located in the posterior wall of mid antrum. (B) Marking around the tumor with argon plasma coagulation. (C) Submucosal injection around the markings. (D) Submucosal incision using an insulated-tip knife. (E) Full-thickness puncture of the muscularis propria layer. (F) Full-thickness dissection of the muscularis propria layer using an insulated-tip knife.

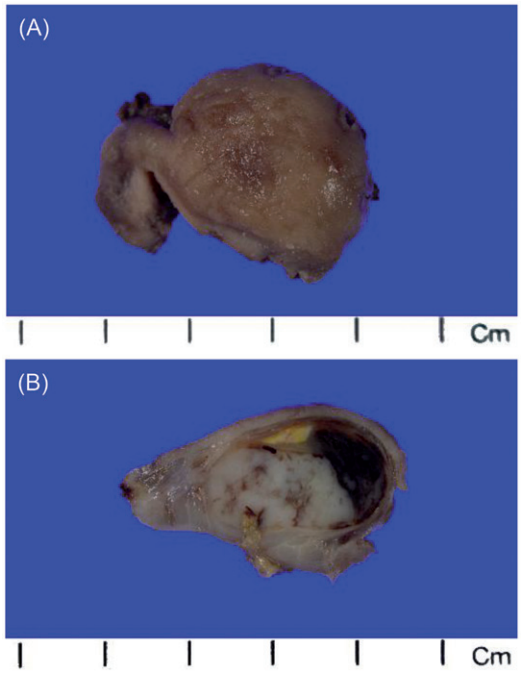

Figure 2. The gross finding of the resected tumor. (A) The tumor with an intact mucosal surface. (B) The cross-section view of the tumor.

on the first day after surgery. If patients were tolerable, a liquid diet was given to them on the second day, followed by a soft diet from the third day. When the patients could tolerate a soft diet for at least two days and did not show any postoperative complications that required in-hospital care, they were discharged.

Assessment of postoperative complications and oral intake was performed in out-patient clinic interview every 3 months for half of a year and at 6 months interval for the following 3 years. Follow-up esophagogastroduodenoscopy and abdominal computed tomography were performed 6 months after surgery to exclude the possibility of any residual primary tumor and to check for recurrence.

Pathologic assessment

All resected tumor specimens were sent to the department of pathology in our hospital and then were paraffin embedded. After sectioning the specimens, hematoxylin and eosin staining and immunohistochemical staining for CD34, CD117 (c-kit), smooth muscle actin, S-100, Desmin, and Vimentin was done. If the specimen was diagnosed as a GIST, a mitotic count under a high-power microscopic field was calculated in order to determine the risk of aggressive behavior according to the classification of Miettinen and Lasota.[15]

Curative resection (R0 resection) was defined as a microscopically margin-negative resection, in which there is no macro/microscopic tumor remnants.[16] Incomplete resection was defined as a failure of complete removal of the tumor with either microscopic margin involvement or macroscopic tumor remnants (R1 or R2 resection).

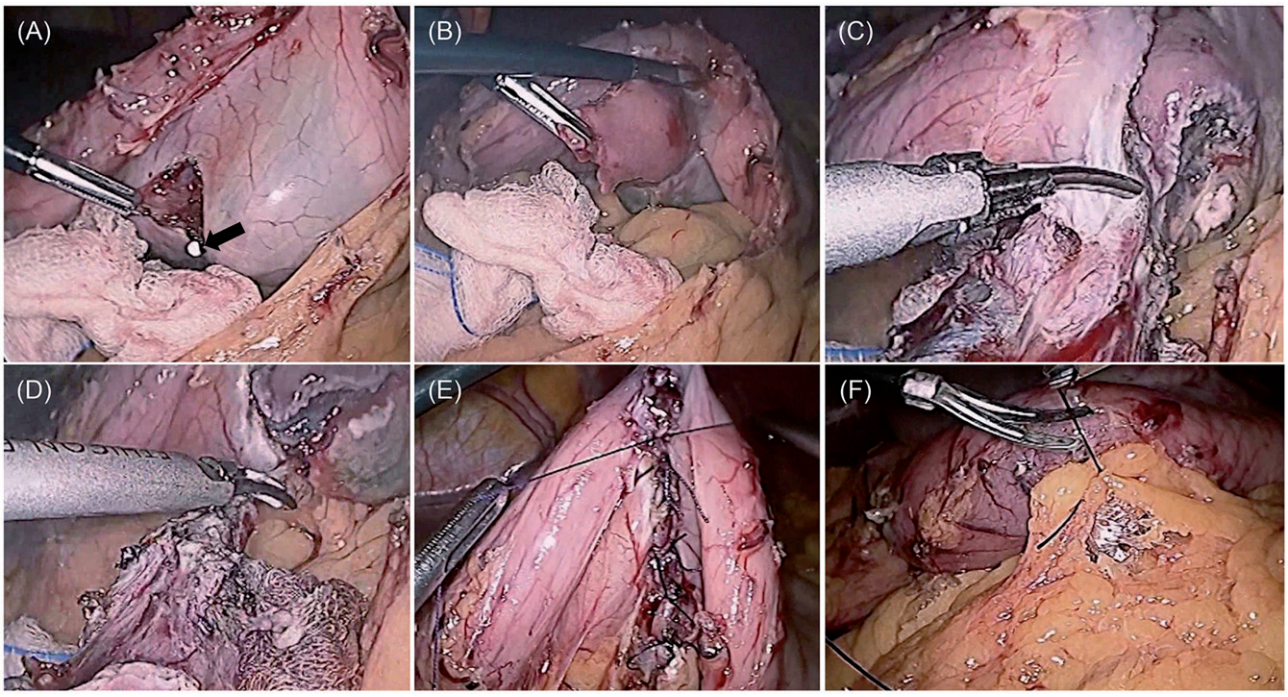

Figure 3. The laparoscopic view of hybrid resection of a gastric subepithelial tumor. (A) Full-thickness resection of the gastric wall around the tumor. (B) The view of the tumor after the endoscopic resection with insulated-tip knife by a half of the margin. (C and D) The resection of the margin around the tumor with an ultrasonic scissor. (E) Laparoscopic perpendicular suture of the resected margin. (F) Application of the patch of mesenteric fat at suture site.

Main outcome measurement

Primary end-point of the study was the success rate of LAEFTR and following laparoscopic closure of the gastric wall defect with achievement of an R0 resection for gastric SETs. In addition, the rate of postoperative complications, total operation time, laparoscopic procedure time, endoscopic procedure time, and the conversion rate to open surgery were evaluated. Laparoscopic procedure time was defined as total operation time minus endoscopic procedure time.

Results

A total of 12 patients were enrolled in our study. The clinical characteristics and preoperative data of all the patients enrolled in this study are shown in Table 1. The median age of the enrolled patients was 51.5 years (24–68) and the number of male and female was same (6 of 12, 50%). The tumors were distributed mainly from low body to proximal antrum (8 of 12 cases, 66.7%), followed by upper body in two patients and mid body/cardia in each one patient. The median size of the tumors in long diameter were 22 mm (21–33). Of the six patients in which preoperative pathologic examination including EUS-guided fine needle aspiration and strip biopsy method were performed, five patients were diagnosed as GIST.

In 4 of 12 patients, the tumors could be identified with laparoscopic view and only LWR was required. The operative results for the remaining eight subjects who underwent LAEFTR were described in Table 2. The tumors were curatively resected in an en-bloc fashion in all the eight patients who underwent LAEFTR. In these eight patients, the median total operation time per person was 127.5 min (110–150), and the median endoscopic and laparoscopic procedure times were 42.5 and 45.0 min [(20–52) and (25–49), respectively]. The intra-operative blood losses were minimal, estimated from 30 to 100 mL. In the final pathologic diagnosis of these eight patients, GIST was diagnosed in four (low risk in the two, intermediate risk in the remaining two), ectopic pancreas in two, leiomyoma in one, and schwannoma in one.

The mean duration of post-operative hospital admission was 4.5 days (3–7) and the median follow-up period was 20 months (6–25). Post-operative complications, such as bleeding, leakage and peritonitis, did not occur in all the eight patients. Symptoms associated with gastrointestinal obstruction or delayed gastric emptying did not occur during follow-up period and there were no structural abnormalities such as stenosis and deformity and tumor recurrence in the

Table 1. Clinical characteristics of the patients.

			Endoscopic and EUS findings				
No.	Gender	Age (years)	Location	Size, length × width (mm)	Ulcer	Pre-operative Histology	Conversion to LWR
1	F	62	Cardia	21 × 10	No	Not done	No
2	M	53	LB/GC	28 × 18	No	GIST	No
3	M	42	LB/GC	25 × 15	No	Not diagnostic	Yes
4	F	68	PA/LC	21 × 20	No	GIST	No
5	F	38	PA/GC	22 × 16	No	Not done	No
6	F	55	UB/AW	20 × 14	No	GIST	Yes
7	M	49	PA/PW	22 × 19	No	Not done	No
8	F	68	UB/GC	22 × 16	No	GIST	Yes
9	F	50	AG/PW	22 × 14	No	GIST	No
10	M	62	MB/LC	20 × 12	No	Not done	Yes
11	M	24	AG/AW	25 × 21	No	Not done	No
12	M	44	AG/AW	33 × 24	No	Not done	No

EUS: endoscopic ultrasonography; LWR: laparoscopic wedge resection; LB: low body; GC: greater curvature; GIST: gastrointestinal stromal tumor; PA: proximal antrum; UB: upper body; AW: anterior wall; PW: posterior wall; AG: angle; MB: mid body; LC: lesser curvature.

Table 2. Outcomes of patients who underwent laparoscopy-assisted endoscopic full-thickness resection.

No.	Gender	Age (years)	Total operation time (endoscopic/laparoscopic procedure), minute	Pre-operative Histology	Final pathology	Mitotic index (/50HPF)	NIH risk classification	Admission period (postoperative), days	ER	CR	Intra-operative bleeding, mL	Post-operative complications
1	F	62	110 (24/44)	Not done	LM			7 (5)	Yes	Yes	50	No
2	M	53	120 (45/25)	GIST	GIST	6–10	Intermediate	7 (5)	Yes	Yes	100	No
4	F	68	130 (41/35)	GIST	GIST	<5	Low	6 (4)	Yes	Yes	50	No
5	F	38	115 (27/39)	Not done	EP			5 (4)	Yes	Yes	100	No
7	M	49	150 (52/47)	Not done	GIST	6–10	Intermediate	6 (5)	Yes	Yes	20	No
9	F	50	150 (45/49)	GIST	GIST	<5	Low	8 (7)	Yes	Yes	50	No
11	M	24	145 (44/47)	Not done	EP			5 (4)	Yes	Yes	50	No
12	M	44	125 (20/46)	Not done	SCW			4 (3)	Yes	Yes	5	No

ER: en-bloc resection; CR: curative resection; LM: leiomyoma; GIST: gastrointestinal stromal tumor; EP: ectopic pancreas; SCW: schwannoma.

follow-up endoscopic examination and abdominal-computed tomography.

Discussion

Various resection techniques using endoscopic devices without laparoscopic assistance have been suggested for the resection of the small-sized gastric SETs. However, the superiority among these modalities remains to be determined. Endoscopic resection methods of upper gastrointestinal SETs, preserving the outer MP layer, were investigated in several studies.[4–9] The standard ESD was reported to achieve the overall complete resection rates of 64–100%, showing the rates of perforation ranged from 0% to 12%.[4–6] In a study about the endoscopic muscularis dissection for upper gastrointestinal SETs originating from the MP layer, 30 of 31 tumors (97%) were completely resected and the rate of perforation was 13%.[7] In two studies about the endoscopic submucosal tunnel dissection, the overall rates of complete resection and complications such as pneumothorax or subcutaneous emphysema were 98% and 8%, respectively.[8,9] However, the rate of complete resection was not consistent among endoscopic resection modalities without laparoscopic assistance, which could be considerably influenced by the technical skill of the endoscopists. Therefore, it is difficult to recommend them as the optimal treatment of all gastric SETs, which still should be considered in highly selected cases.

The laparoscopic resections have been accepted as a traditional choice of treatment for gastric SETs originating from the MP layer such as GISTs and leiomyomas. In a majority of cases, the wedge resection methods were performed and the resection margins were almost tumor-negative in the studies about laparoscopic surgery of gastric GISTs.[17–20] However, the chances of an inaccurate resection are higher during laparoscopy, because laparoscopic resections can only be done in a linear manner without taking the margin of the tumors into account.

Recently, hybrid resection methods, such as the laparoscopic and endoscopic cooperative surgery and LAEFTR, have been suggested as an alternative treatment option for gastric SETs.[11–13] Hybrid resection methods showed more consistent and better results than resection methods using the endoscopic procedure alone all the while preserving the outer MP layer. The rates of curative resection were 100% in almost all studies about hybrid resections for treatment of gastric SETs,[13,21,22] and significant major procedure-related complications did not nearly occur. However, there is no comparative prospective study among hybrid resection modalities.

LAEFTR is an emerging technique applied to the resection of gastric neoplasms, which is classified as a kind of hybrid NOTES (natural orifice transluminal endoscopic surgery). The combination of endoscopic and laparoscopic manipulation in LAEFTR allows an optimal resection of gastric SETs without excessive removal of the unaffected stomach tissue surrounding the tumor. LAEFTR could be particularly recommended as the optimal resection method of intraluminal growing gastric SETs which are not visible in laparoscopic view.

This study showed that LAEFTR was a feasible and safe method of treatment for gastric SETs originating in the MP layer. The rates of en-bloc resection and curative resection were 100%. No major procedure-related complications such as anastomotic leakage or stricture occurred after surgery. The mean duration of postoperative hospital admission was 4.5 days, which is shorter than that in a previous study applying the same resection technique.[13] Oral diet was resumed 2 days after surgery in almost all patients and there were no significant complications, for which additional treatment was needed, in all enrolled patients during the follow-up period. In this study, one patient who had the SET located in cardia received LAEFTR and the post-operative cardiac stenosis did not occur. In LAEFTR, the tumors are delicately resected with the endoscopic knives and a Harmonic Scalpel along the incision line around the tumors. And then, the suture is performed in a perpendicular direction not to induce narrowing of the gastric lumen, which could minimize the risk of cardiac stenosis.

In this study, the endoscopic incision of the gastric wall was carried out on about half of the tumor circumference, and then the remaining half was incised and resected laparoscopically, because a full circumferential incision of the tumor using endoscopy alone is not easy as the amount of leaked air increases, resulting in the gastric lumen further collapsing and making tumor resection more difficult. When the endoscopic transmural dissection of half of the tumor circumference is done, the full mucosal incision line around the tumor becomes laparoscopically visible, making laparoscopic resection easier. When considering the results in this study and previous reports about hybrid resection methods, LAEFTR was shown to have more advantages than endoscopic resection methods alone preserving the underlying the MP layer or endoscopic full-thickness resection without laparoscopic assistance. In an oncologic view, hybrid resections such as

LAEFTR are more effective in improving the rate of R0 resection than endoscopic resection alone.

Another important issue is about how to seal a purposely perforated gastric wall elaborately. In two studies where the endoscopic resection without laparoscopic assistance were done for the treatment of gastric SETs, the efficacy of clipping methods using conventional metal clips and the over-the-scope clips (OTSCs) were analyzed.[18,23,24] No procedure-related complications were reported to occur after clipping in both studies. However, a major limitation of clipping is that the size of the perforated area could be larger than the range, up to which conventional metal clips or the OTSCs can be opened.[24] When the perforated area is larger than 1 cm, they are near impossible to be closed with a single conventional clip. In such cases, multiple conventional metal clips are required, but are somewhat strenuous for the endoscopists. Also, the OTSCs could not be utilized for perforated areas larger than 2 cm.[24] In addition, the larger the perforated area the more difficult it is to secure a clear view of the area that needs to be clipped, because intra-gastric air has leaked into the peritoneal cavity after gastric perforation.

Therefore, the endoscopic clipping methods need to be improved, when compared with laparoscopic sealing methods. In one study where the conventional metal clips were applied to the perforated area of the gastric wall, the omental patch method after intra-gastric air suction was utilized for the sealing of large perforated area, which requires a delicate endoscopic performance feasible only by highly experienced therapeutic endoscopists.[21] In this study, the laparoscopic suture, which is not influenced by the size or location of the perforated area of the gastric wall, was done in the oral–anal direction along the longitudinal axis of the stomach, to secure more space for the passage of food material.

With a meticulous review of previous studies, we suggest LAEFTR as the optimal treatment modality among recently developed innovative methods for the resection of gastric SETs originating in the MP layer. It offers the opportunity to resect the tumors in the precise and safe manner, compared with the other resection modalities. The additional advantage of LAEFTR is the simplicity of the resection manner, which is not difficult than standard ESD. In our experience, we could proficiently perform LAEFTR only after several experiences. If the gastric SETs are located at the body or the fundus which has more space, the risk of deformity and stricture is not problematic even after LWR. However, if the mass lesions are located at the antrum or near the esophago-gastric junction which has less space, LAEFTR could give a favorable outcome than LWR, because resection of the stomach tissue surrounding the tumor could be minimized to reduce deformity and maintain its function of the remnant stomach.

Hybrid resection modalities have shown relatively favorable outcomes without any significant complications. However, although there have been no reported cases yet, occurrence of local tumor seeding should be taken into consideration due to a possible rupture of tumor capsule during the endoscopic dissecting procedure that require endoscopic knives, or using laparoscopic grasping forceps for everting the lesion into the peritoneal space, or the laparoscopic dissection procedure of the remaining circumference. One study on laparoscopic surgery, which analyzed the outcomes of primary GISTs greater than 3 cm with microscopically positive margins (R1 resection), reported that the 3-year survival rate without recurrence for the patients with tumor rupture was significantly lower than in the patients without rupture (60% vs. 80%, hazard ratio 3.58; 95% confidence interval 1.65–7.79; $p = .001$).[10] However, there is no data about tumor seeding after laparoscopic surgeries in SETs less than 3 cm with microscopically positive margins so far, requiring further investigative studies.

We should address the limitation of our pilot study. The number of enrolled patients in our study is quite small. And, pre-operative pathologic diagnosis was determined only in three of eight patients who underwent LAEFTR, which led to unnecessary resection for four patients who were finally diagnosed as ectopic pancreas. Finally, we did not perform comparative analysis with other similar resection modalities, which need further investigation in the future.

In conclusion, LAEFTR is the feasible, safe and effective treatment modality in the treatment of gastric SETs originating in the MP layer, especially with an intraluminal growth pattern where their resection margins are difficult to define under laparoscopic guidance alone or which is located in the gastric antrum or near esophago-gastric junction, although further large-scale randomized prospective studies are required.

Disclosure statement

All of the authors have no conflicts of interest.

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