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Cutting edge of endoscopic full-thickness resection for gastric tumor

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Abstract

Recently, several studies have reported local full-thickness resection techniques using flexible endoscopy for gastric tumors, such as gastrointestinal stromal tumors, gastric carcinoid tumors, and early gastric cancer (EGC). These techniques have the advantage of allowing precise resection lines to be determined using intraluminal endoscopy. Thus, it is possible to minimize the resection area and subsequent deformity. Some of these methods include: (1) classical laparoscopic and endoscopic cooperative surgery (LECS); (2) inverted LECS; (3) combination of laparoscopic and endoscopic approaches to neoplasia with non-exposure technique; and (4) non-exposed endoscopic wall-inversion surgery. Furthermore, a recent prospective multicenter trial of the sentinel node navigation surgery (SNNS) for EGC has shown acceptable results in terms of sentinel node detection rate and the accuracy of nodal metastasis. Endoscopic full-thickness resection with SNNS is expected to become a treatment option that bridges the gap between endoscopic submucosal dissection and standard surgery for EGC. In the future, the indications for these procedures for gastric tumors could be expanded.

Key words: Gastrointestinal stromal tumor; Early gastric cancer; Full-thickness resection; Laparoscopic and endoscopic cooperative surgery; Sentinel node navigation surgery

Core tip: Several studies have investigated local full-thickness resection techniques using flexible endoscopy for gastric tumors. These techniques are advantageous because a resection line can be determined more precisely using intraluminal endoscopy. Thus, it is possible to minimize the resection area and subsequent deformity, and better secure the surgical margins. In the near future, endoscopic full-thickness resection is expected to become a treatment option that bridges the gap between endoscopic submucosal dissection and standard surgery for gastric tumors.

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INTRODUCTION

Laparoscopic wedge resection (LWR) has been accepted as a minimally invasive surgical technique for gastric tumors such as gastrointestinal stromal tumor (GIST)[1], early gastric cancer (EGC) without the risk of lymph node metastasis[2,3]. However, patients frequently experience severe deformity and gastric stasis as a result of excessive gastric resection. This occurs because identification of the proper incision line is complicated. From this point of view, several studies have reported that endoscopic submucosal dissection (ESD) and endoscopic submucosal enucleation are feasible for the resection of gastric tumors in the muscularis propria[4,5]. Furthermore, ESD has performed for the diagnosis of suspected submucosal EGC. However, some tumors are resected incompletely because they have positive surgical margins; thus, the risk of recurrence exists[6]. Therefore, a full-thickness resection would be more appropriate to secure the surgical margins. This suggests the need for function-preserving or reductive surgeries that bridge the gap between ESD and standard surgery. Recently, some publications have described local resection techniques using peroral flexible endoscopy. Endoscopic full-thickness resection (EFTR) of the gastric wall using a snaring technique has been applied for gastric subepithelial tumors[7-9]. In addition, Hiki *et al*[10] reported that classical laparoscopic and endoscopic cooperative surgery (classical LECS) provides an alternative gastric wedge resection. However, these procedures (EFTR and classical LECS) have inherent risks of peritoneal infection and cancer cell seeding because intentional perforation of the gastric lumen is required during the procedures. As a result, some procedures [*e.g.,* inverted LECS[11], a combination of laparoscopic and endoscopic approaches to neoplasia with non-exposure technique (CLEAN-NET)[12] and non-exposed endoscopic wall-inversion surgery (NEWS)[13]] have been developed to mitigate these risks. These techniques are advantageous because a more precise resection area can be determined using intraluminal endoscopy, thus minimizing the resection area. This will result in less deformity and better surgical margins.

In the current review, recent developments related to full-thickness resection using flexible endoscopy for gastric tumors are presented and discussed.

EFTR WITHOUT LAPAROSCOPIC ASSISTANCE

Endoscopic full-thickness resection of the gastric wall using a snaring technique has been applied for gastric subepithelial tumors[7]. Nevertheless, this technique has limitations from the perspective of the localization and size of the lesion. Ikeda *et al*[14]. reported EFTR using an ESD technique with a sewing method and have shown that it is possible to resect larger specimens. In addition, Zhou *et al*[8] and Feng *et al*[15] reported successful resection of gastric subepithelial tumors originating from the muscularis propria layer[8,15] (Table 1).

Table 1 Representative publications reporting endoscopic full-thickness resection for upper gastrointestinal tumors

Ref.	*n*	Mean operation time (min)	Mean tumor diameter (mm)	Complete resection rate (%)	Complication rate (%)
Zhou *et al*[8]	26	105	28	100	0
Feng *et al*[15]	48	60	16	100	0
Huang *et al*[16]	35	90	28	100	0
Schmidt *et al*[17]	31	60	20.5	90.3	9.7 (perforation)
Guo *et al*[9]	23	40.5	12.1	100	0

After the periphery of the lesion is marked endoscopically, a solution is injected into the submucosal layer circumferentially. A circumferential incision is then made to the depth of the muscularis propria around the lesion using ESD devices and techniques. Next, the serosal layer around the lesion is incised using ESD devices to create an intentional perforation. The tumor, including the surrounding muscularis propria and serosa, is subsequently removed using the snare. Finally, the gastric wall defect is closed with several metallic clips (Figure 1).

There are difficulties associated with these techniques. For example, it is unknown whether a large iatrogenic perforation can be successfully closed using the endoscopic technique. Guo *et al*[9] have reported the safety and feasibility of the over-the-scope clip system for the closure of gastric defects following EFTR. After all, EFTR is expected to prevent the severe complications can occur due to iatrogenic perforation. Although EFTR seems to be an effective and minimally invasive treatment for patients with gastric subepithelial tumors, it is necessary to demonstrate the efficacy and safety of EFTR in a large number of cases.

CLASSICAL LECS

Hiki *et al*[10] reported that the LECS technique provides an alternative gastric wedge resection for the removal of GISTs, and combines gastrointestinal endoscopy and laparoscopy. The advantage of this technique is that it avoids excessive resection of the gastric wall because a resection line can be determined more precisely using intraluminal endoscopy.

The periphery of the lesion is first marked endoscopically, and after a submucosal injection around the lesion, a circumferential incision is made using ESD devices and techniques. Then, an artificial perforation

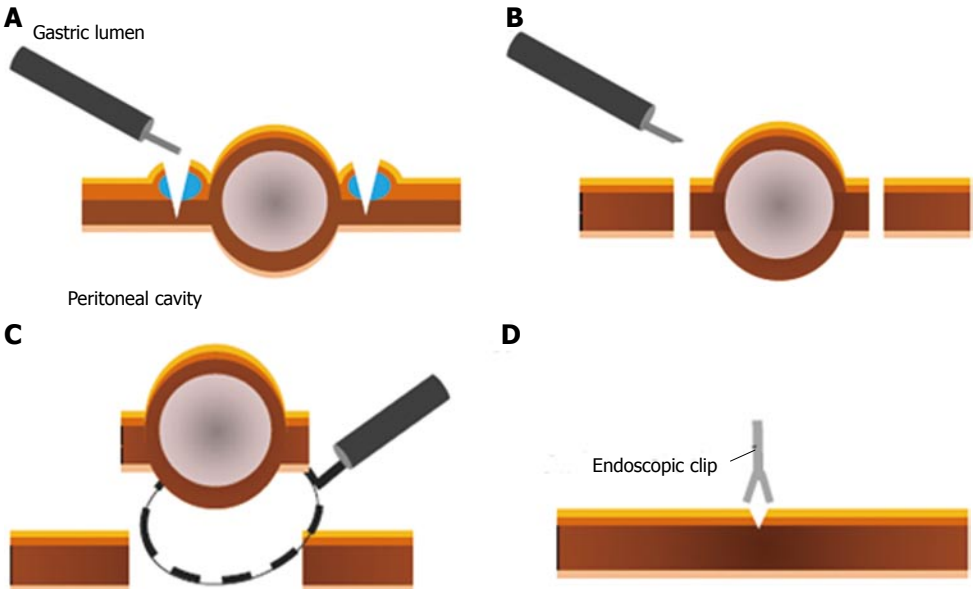

Figure 1 Illustration of the procedure for endoscopic full-thickness resection without laparoscopic assistance. A: A circumferential incision is made to the depth of the muscularis propria around the lesion using endoscopic submucosal dissection (ESD) devices and techniques; B: After intentional perforation, the serosal layer around the lesion is incised using ESD devices; C: The tumor, including the surrounding muscularis propria and serosa, is removed using the snare; D: The gastric wall defect is closed with several metallic clips.

is performed from the inside of the stomach and a seromuscular incision is performed, as much as possible, with laparoscopic assistance. Next, a laparoscopic incision of the remaining seromuscular layer is performed. Finally, the defect closure of the gastric wall is performed by laparoscopic linear staplers or a laparoscopic hand sewn suture technique[16,17] (Figure 2).

Some pilot studies have reported the feasibility of LECS for GISTs, and have presented favorable results[18-20]. This procedure is also feasible for lesions that cannot be treated with LWR[1,21] (*e.g.,* the esophagogastric junction)[22]. However, there is a major limitation associated with classical LECS. This technique requires opening the gastric wall, and the gastric lumen is opened to the abdominal cavity. As a result, gastric contents (*e.g.,* bacteria and tumor cells) flow into and contaminate the clean peritoneal cavity, increasing the risk of bacterial contamination and dissemination of peritoneal tumor cells.

INVERTED LECS

As described above, there are several drawbacks associated with classical LECS especially for gastric cancer. Therefore, a modified LECS procedure, referred to as inverted LECS, was developed to prevent the implanting of tumor cells[11].

The procedure, from placing the markings to performing the artificial perforation, is similar to the classical LECS. To prevent contact between the tumor and the visceral tissue, the gastric wall is pulled up circumferentially to the incision line as a crown using some stitches. Then, the seromuscular layer is dissected using ESD or laparoscopic devices around the incision line of the submucosal layer. The tumor is then resected into the abdominal cavity and the specimen is retrieved perorally. Finally, the gastric wall defect is closed by laparoscopic linear staplers.

This procedure was developed to prevent stomach contents from spilling into the clean abdominal cavity. However, since the gastric lumen is opened to the peritoneal cavity, there is still a risk of gastric content contamination. Furthermore, there is a risk of cancer recurrence caused by instrument contact.

CLEAN-NET

CLEAN-NET is another promising non-exposure method[12]. After mucosal markings are made endoscopically around the tumor, the mucosal layer is fixed to the seromuscular layer with four full-layer stay sutures, and a sub-mucosal cushion is created circumferentially using an endoscopic injection. The seromuscular layer is then dissected laparoscopically around the four stay sutures. Consequently, the full-layer specimen and the mucosal layer that surrounds it are lifted by the stay sutures. Finally, the specimen is resected using a linear stapler (Figure 3). The CLEAN-NET is useful as a non-exposure technique for full-thickness resection.

NEWS

NEWS was developed as a novel, full-thickness resection technique, without intentional perforation[13,23,24]. With this procedure, markings are made around the tumor on the mucosa while serosal markings are made laparoscopically. The serosal markings are made by pressing on the gastric wall, on the side opposite the mucosal markings. A sodium hyaluronate solution, that includes a small amount of indigo carmine dye, is

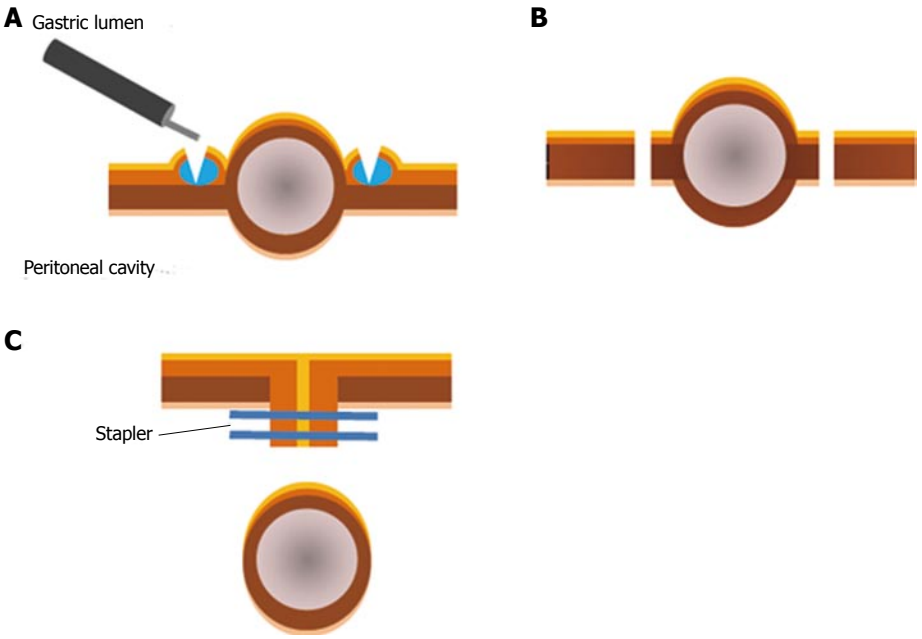

Figure 2 Illustration of the procedure for classical laparoscopic and endoscopic cooperative surgery. A: A circumferential incision is made using endoscopic submucosal dissection (ESD) devices and techniques; B: An artificial perforation is performed from the inside of the stomach and a seromuscular incision is performed along the incision line with laparoscopic assistance. A laparoscopic incision of the remaining seromuscular layer is performed; C: The defect closure of the gastric wall is performed by laparoscopic linear staplers.

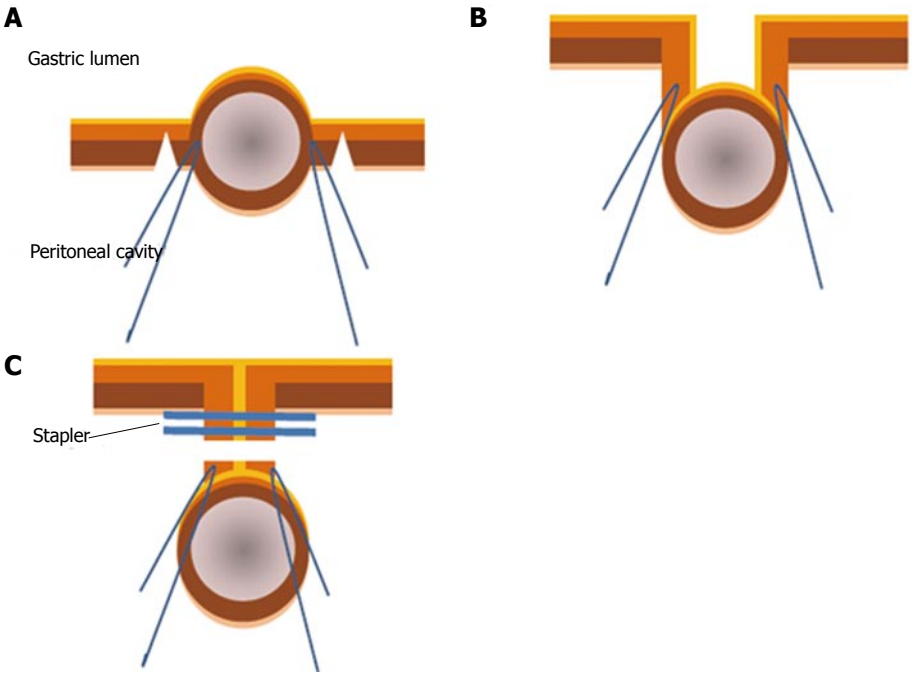

Figure 3 Illustration of the procedure for a combination of laparoscopic and endoscopic approaches to neoplasia with non-exposure technique. A: Seromuscular layer is dissected using a laparoscopic electrocautery knife; B: Full-layer specimen is lifted by the stay sutures; C: Full-layer specimen is resected using a linear stapler.

endoscopically injected into the submucosal layer circumferentially. A circumferential seromuscular incision is performed laparoscopically around the serosal markings. After a flap is created by cutting the submucosa deeper toward the outside, the seromuscular layers are linearly sutured with the lesion inverted toward the inside of the stomach. Prior to the suturing, a laparoscopic surgical sponge is inserted as a spacer between the serosal layer of the inverted lesion and the suture layer. This is done to provide counter-traction to the mucosa and prevent cutting of the suture. Finally, the circumferential mucosal incision and the subsequent incision of the remnant submucosal tissue are made a few millimeters outside of the mucosal markings around the inverted

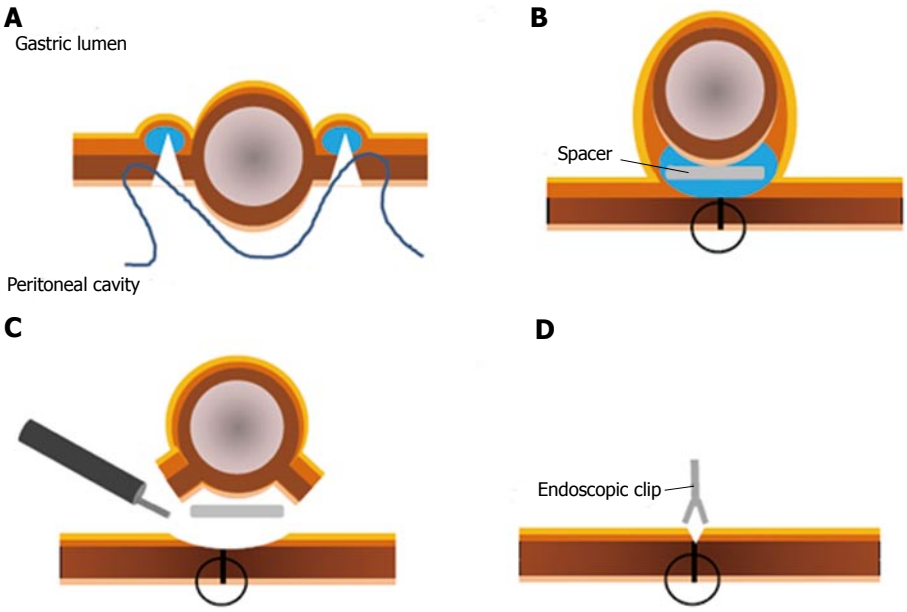

Figure 4 Illustration of the procedure for non-exposed endoscopic wall-inversion surgery. A: circumferential seromuscular incision is performed laparoscopically outside the serosal markings after endoscopic submucosal injection; B: seromuscular layers are linearly sutured with the lesion inverted toward the inside of the stomach. A surgical sponge as a spacer is inserted between the serosal layer of the inverted lesion and the suture layer; C: Circumferential mucosal incision and the remnant submucosal incisions are made using ESD devices and techniques; D: Defect is closed with several metallic clips. ESD: Endoscopic submucosal dissection.

Table 2 Comparison of each procedure

	Instruments	Indication for EGC	Retrieval route	Intentional gastric perforation	Advantage	Limitation
EFTR	Endoscopy only	No	Transroral	Required	Simple methods using intraluminal endoscopy only	Risk of contamination, endoscopic skills required
Classical LECS	Endoscopy = laparoscopy	No	Transabdominal	Required	Accurate to determine the resection line, laparoscopic assistance	Risk of contamination Risk of contact to tumor surface
Inverted LECS	Endoscopy = laparoscopy	Indefinite	Transoral	Required	Accurate to determine the resection line, laparoscopic assistance	Risk of contact to cancer surface, tumor size
CLEAN-NET	Endoscopy < laparoscopy	Yes	Transabdominal	Not required	No transluminal communication	Excessive resection of the mucosa, difficult to determine the resection line
NEWS	Endoscopy = laparoscopy	Yes	Transoral	Not required	Accurate to determine the resection line, laparoscopic assistance, no transluminal communication	Tumor size, experience required, time-consuming

EFTR: Endoscopic full-thickness resection; LECS: Laparoscopic and endoscopic cooperative surgery; CLEAN-NET: Combination of laparoscopic and endoscopic approaches to neoplasia with a nonexposure technique; NEWS: Nonexposed endoscopic wall-inversion surgery; EGC: Early gastric cancer.

lesion using ESD techniques. The resected specimen and the spacer are retrieved perorally and the mucosal edges are closed with several endoscopic clips (Figures 4 and 5).

The NEWS technique has been developed as a full-thickness resection method without transluminal communication and is similar to the CLEAN-NET. It is a non-exposure technique. However, there are several differences between the two procedures. First, the seromuscular hand suturing and circumferential mucosal incision can be skipped in CLEAN-NET, which results in a shorter procedural time than that for NEWS. Secondly, the incision line is determined from the serosal side; as a result, proper mucosal incision could be complicated to determine resulting in a relatively large resection area. However, due to the lower risk of peritoneal cavity infection and the seeding of tumor cells, NEWS has already been clinically introduced for gastric subepithelial tumors as well as gastric cancers at selected hospitals[24]. This procedure is technically feasible and, theoretically, safe.

APPLICATION TO GASTRIC CANCER

ESD is widely accepted as a minimally invasive curative treatment for early stage gastrointestinal cancer[25-27]

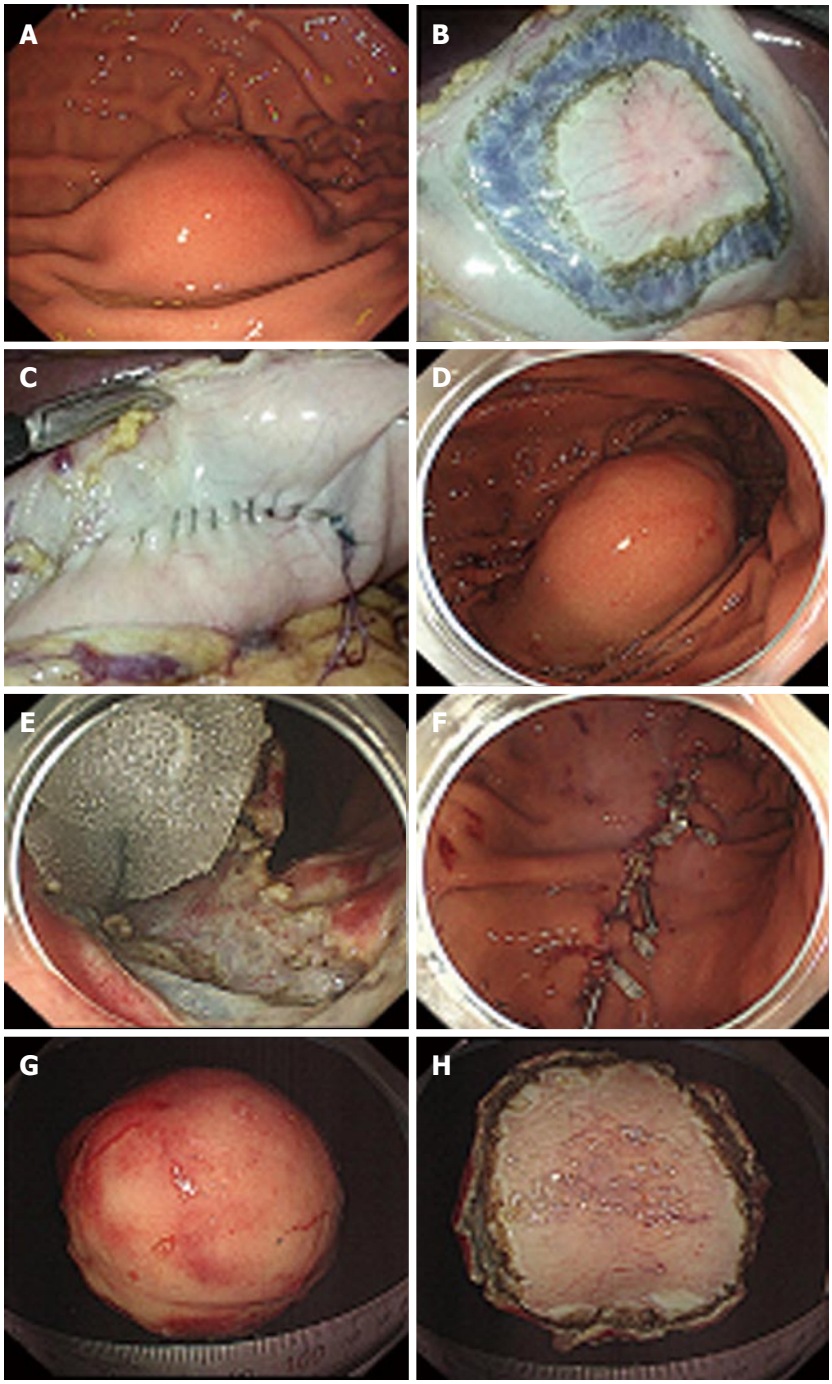

Figure 5 Procedures of non-exposed endoscopic wall-inversion surgery. A: Protruding submucosal lesion is seen at the greater curvature of the middle gastric body; B: Circumferential seromuscular incision is made outside the serosal markings after endoscopic submucosal injection; C: Lesion is inverted with a surgical sponge used as a spacer; D: Massive protrusion of the inverted tissue; E: Surgical sponge as a spacer and a suturing line during endoscopic mucosal incision; F: Mucosal clipping after the resection; G: Resected specimen: Mucosal side; H: Resected specimen: Serosal side.

that enables the preservation of function and maintains the patients' quality of life. However, ESD still requires a skilled and experienced surgeon for large lesions located at the greater curvature of the upper gastric body and fornix, and for lesions with severe ulcerative changes. In these situations, ESD has a higher incidence rate of complications such as perforation and bleeding. Furthermore, ESD may be associated with longer operation times[28]; therefore, LECS may be an alternative treatment option especially for lesions difficult to resect by ESD[11].

In contrast, EGC with possible lymph node metastasis should be treated with gastrectomy with wide resection of the regional lymph nodes because the presence and site of lymph node metastasis are unclear. Approximately 10%-20% of patients with EGC, especially those with deep submucosal invasion, have lymph node metastasis[29]. In other words, the incidence of node-negative gastric cancer accounts for at least 80% of all EGCs and therefore, most of the patients

with EGC have undergone an unnecessarily wide gastrectomy with lymphadenectomy. If node-negative gastric cancer is confirmed, local resection (*e.g.,* full-thickness resection) might be the best option.

Sentinel node navigation surgery (SNNS) is expected to be able to diagnose lymph node metastasis intraoperatively, and this could result in minimally invasive and function-preserving gastrectomy with selective lymphadenectomy[30]. Theoretically, the sentinel node (SN) is the first lymph node or group of nodes capable of draining cancer cells and is considered the first site of metastasis along the route of lymphatic drainage. However, it remains controversial whether the SN concept is feasible in EGC. In response, the Japan Society of Sentinel Node Navigation Surgery conducted a prospective multicenter trial to confirm the SN concept. It reported that patients with clinical T1N0 ($\leqslant$ 4 cm) gastric cancer can undergo sentinel node mapping and biopsy without limitation of tumor location[31]. Currently, surgical treatment of cT1N0 gastric cancer, of $\leqslant$ 4 cm, can be individualized on the basis of the SN concept. Furthermore, some studies have reported that in the absence of metastasis to the SNs, a surgery that combines ESD and SNNS[32] may be adequate. However, ESD cannot guarantee secure vertical margins or accurate preoperative diagnosis of tumor invasion. Hence, for submucosal EGC, a full-thickness resection would be more appropriate to secure the vertical margins and identify intramural cancer cells. Abe *et al*[33] first reported EFTR for EGC under laparoscopic guidance, combined with lymphadenectomy. Similarly, Hur *et al*[34] reported laparoscopy-assisted endoscopic full-thickness resection with sentinel node navigation surgery. However, as previously mentioned, these procedures require opening of the gastric wall, thus opening the gastric lumen to the peritoneal cavity. As a result, cancer cells may spill into the peritoneal cavity. Consequently, peritoneal dissemination of cancer cells as well as bacterial contamination during the procedure might occur. Therefore, it is desirable to use a non-exposure technique to prevent bacterial contamination and peritoneal dissemination of tumor cells. Hence, full-thickness resection such as NEWS and CLEAN-NET, in combination with sentinel node basin dissection, may be an ideal treatment that bridges the gap between ESD and standard surgery with respect to the invasiveness of the treatment[35,36] (Table 2).

CONCLUSION

The endoscopic full-thickness resection for upper gastrointestinal subepithelial tumors and EGC has been developed as a novel and minimally invasive surgery. In particular, NEWS with sentinel node basin dissection may be an ideal, minimally invasive, and function-preserving gastrectomy with selective lymphadenectomy for EGC. However, reports of these procedures are limited to case reports. Pilot studies need to be performed, and the long-term efficacy of these procedures need to be clarified. Therefore, further studies such as prospective clinical trials with a large number of patients are required to show the feasibility of these treatment methods, especially with regard to safe and complete resection. In the near future, the concept of endoscopic full-thickness resection is expected to become a treatment option that bridges the gap between ESD and standard surgery for subepithelial tumors and EGC.

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