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Recent Advances in Endoscopic Treatment Techniques for Subepithelial Lesions

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Recent advancements in endoscopic techniques have resulted in greater adoption of minimally invasive methods for diagnosing and treating gastric subepithelial lesions (SELs), significantly reducing the reliance on traditional surgery. Numerous studies have demonstrated that the endoscopic removal of gastric SELs is safe and effective, especially for tumors with low malignant potential. Ongoing improvements in endoscopic tools and procedural innovations continue to enhance therapeutic outcomes and reduce complication rates. This review explores the current endoscopic treatments for gastric submucosal tumors, emphasizing recent technological advancements.

Keywords Endoscopic surgical procedures; Stomach neoplasms; Minimally invasive surgical procedures.

INTRODUCTION

Surgical resection is the primary treatment for gastric subepithelial lesions (SELs). However, as endoscopic techniques have advanced, endoscopic resection has emerged as a practical alternative to traditional surgical methods. Recently, endoscopic resection techniques have been employed to treat SELs, including endoscopic submucosal dissection (ESD), submucosal tunneling endoscopic resection (STER), endoscopic full-thickness resection (EFTR), endoscopic band ligation (EBL), and laparoscopic and endoscopic cooperative surgery (LECS).

Recent studies have examined the safety and efficacy of endoscopic treatments for SELs.[1,2] These methods have proven safe and effective in managing SELs, including gastric SELs arising from the muscular propria (MP) layer. However, consensus has not yet been reached regarding the optimal follow-up strategy or ideal tumor size threshold for endoscopic resection.

Endoscopic resection offers benefits such as shorter procedure times and hospital stays, and less blood loss compared to laparoscopic surgery. It has achieved similar success and complication rates. Consequently, endoscopic resection is broadly regarded as a valid alternative treatment for gastric SELs.[3-5] This review summarizes the recent progress in endoscopic therapies for gastric SELs (Table 1).

ENDOSCOPIC TREATMENT OF GASTRIC SELs

Endoscopic submucosal dissection

ESD was originally used for the resection of early gastrointestinal cancers and has recently been used for SELs (Fig. 1). An et al.[6] analyzed data from 168 patients who underwent ESDs for gastrointestinal stromal tumors (GISTs) located in the MP layer. The en bloc resection rate was 100%, with no recurrence or metastases during 25 months. Most lesions were observed in the gastric fundus. The median tumor size was 1.5 cm, ranging from 0.5 to 6.0 cm, with a consistent shape in 154 patients. The average procedure duration was 46.5 min (range 33–181 min). Gastrointestinal wall defects occurred in 71 patients (42.3%), and delayed hemorrhage occurred in two (1.2%) treated with clips. Of these, 117 were at very low risk, 37 were at low

Table 1. Comparison of endoscopic techniques for gastric subepithelial lesions

Technique	Indications	Advantages	Limitations	Procedure time
ESD	SELs in muscularis propria, esp. small to moderate-sized GISTs	High en bloc resection rate (92%–100%) Suitable for small lesions	High risk of gastric wall defect Perforation risk Technical difficulty	43.97±13.0 minutes
EBL	Small gastric SELs, especially low-risk GISTs	Simple technique Low risk of perforation Short procedure time	Limited to small tumors Inaccurate histological margin evaluation Cap size limits use	48 minutes (SD not reported)
EFTR	GISTs or SELs from muscularis propria requiring full-thickness removal	R0 resection possible Avoids laparoscopic surgery Seals wall defect with OTSC/OverStitch	Technically demanding Risk of peritonitis Requires suturing device	52.0±approx. 8–12 minutes (varies)
STER	SELs in esophagus and gastric cardia	Preserves mucosa Lower risk of leakage Shorter recovery	Not ideal for fundus or >4 cm lesions Technically demanding	92.1±40.8 minutes
LECS	Larger SELs, lesions in difficult locations (e.g., EG junction, cardia)	Precise localization with endoscopy Minimal resection of healthy tissue Multidisciplinary	Risk of tumor seeding (classical LECS) Requires OR, surgical team	190.2±66.8 minutes

Data are presented as means±standard deviations or medians.
ESD, endoscopic submucosal dissection; EBL, endoscopic band ligation; EFTR, endoscopic full-thickness resection; STER, submucosal tunneling endoscopic resection; LECS, laparoscopic and endoscopic cooperative surgery; SELs, subepithelial lesions; GISTs, gastrointestinal stromal tumors; esp., especially; EG, esophagogastric; OTSC, over-the-scope clip system; OR, operating room; SD, standard deviation.

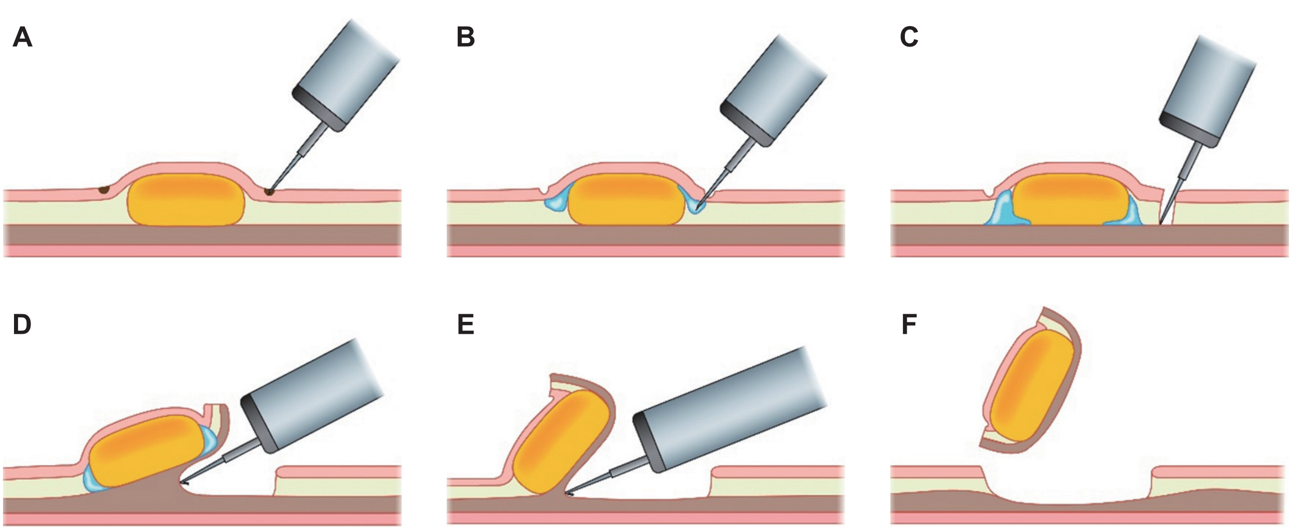

Fig. 1. Endoscopic submucosal dissection. Marking (A), injection (B), mucosal injection (C), dissection (D), continued dissection (E), and complete resection (F).

risk, and 14 were at mild risk. No recurrence or metastases occurred during 6–67 months of follow-up. Tumor shape was an independent risk factor for wall defects. In long-term follow-up data (mean follow-up 36.15±12.92 months), 60 consecutive patients underwent endoscopic resections (including 25 ESDs),[7] with an average procedure duration of 43.97 min. Two patients had approximately 200 mL of bleeding, which was successfully controlled using hemostatic forceps. Perforations after ESDs occurred in four cases (4/25), sized 2–11 mm, and were treated with endoscopic clips without surgery. One patient experienced esophageal mucosal injury during the removal of a large tumor. Average hospital stay was 6.50±3.06 days (range 3–21 days). Among the patients, 44 (73.3%) had very low risk, 10 (16.7%) had low risk, 5 (8.3%) had moderate risk, and 1 (1.7%) had high risk. During follow-up, one patient had a recurrence and underwent surgery after 32 months; no other patients showed recurrence or metastases. However, considering the malignant potential of GISTs, ESD may lead to tumor recurrence or intraperitoneal transplantation due to gastric wall defects, tumor spread, or tumor rupture.[8,9] To avoid complications such as recurrence, it is crucial to accurately identify the lesion location using endoscopic ultrasonography, classify the tumor type, and choose an appropriate procedure based on the lesion's risk.

Endoscopic band ligation

EBL has been traditionally used to treat esophageal varices and gastric submucosal tumors (Fig. 2). The risk of complications can be reduced by endoscopic resection with EBL, particularly when an electrosurgical unit is involved. Since most GISTs originate in the MP layer, endoscopic resection with electosurgical unit may increase the risk of serious complications such as bleeding and rupture. Patients initially treated with EBL for small GISTs (or ≤1.5 cm in size) were analyzed.[10] Endoscopic ligation was conducted in 29 patients, achieving a 96% complete resection rate. There were no complications such as perforation, although one patient experienced bleeding. The follow-up period was 32 months, and no recurrence was noted.

Endoscopic enucleation assisted by EBL was used to remove GISTs located in the MP in 21 patients.[11] The authors utilized endoloop ligation or modified elastic bands for the procedure. The average treatment duration was 48 min. There were no complications, such as perforations, significant bleeding, or peritonitis, following the procedure. All tumors were entirely removed, and no recurrence was observed during the 21-month follow-up period.

EBL is generally indicated, especially in lesions where access and suctioning are feasible. However, the disadvantages of endoscopic resection with EBL include the limited size of resectable GISTs owing to the cap used and the inability to perform precise post-resection histological evaluations. However, small GISTs tend to have a lower likelihood of malignancy. Therefore, EBL resection is a viable option, especially when considering the patient's age and overall health.

Endoscopic full-thickness resection

EFTR was initially developed for treating rectal and duo-

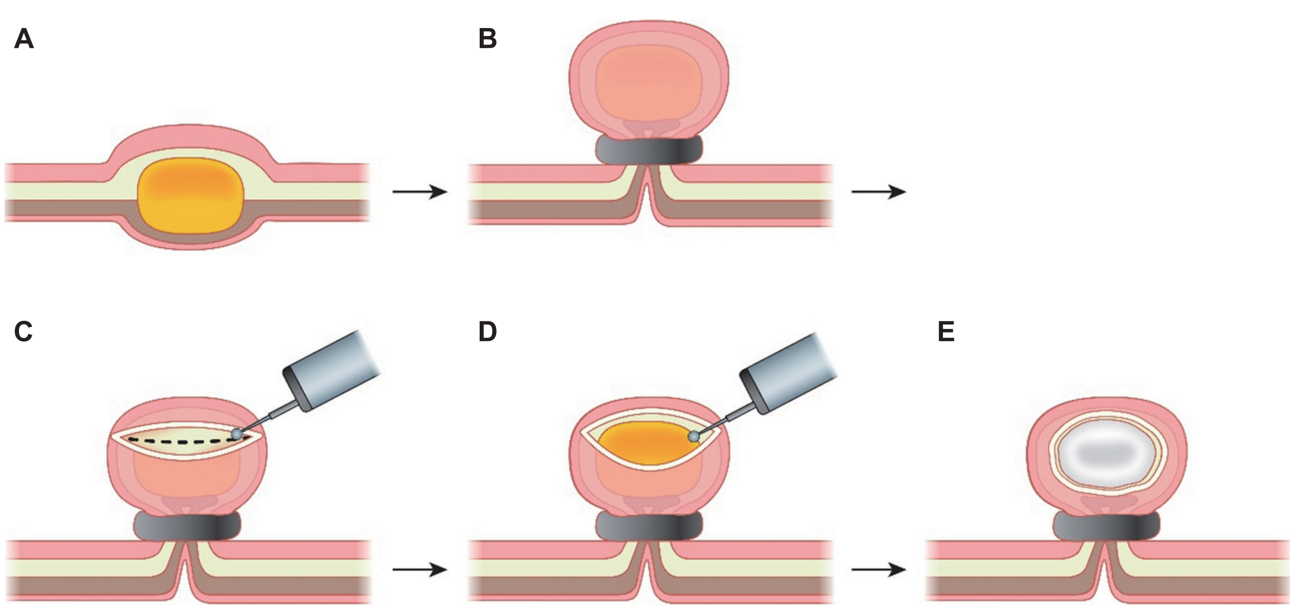

Fig. 2. Endoscopic band ligation. Subepithelial tumor originating from the muscularis propria layer (A), band ligation (B), dissection (C), continued dissection (D), and complete resection (E).

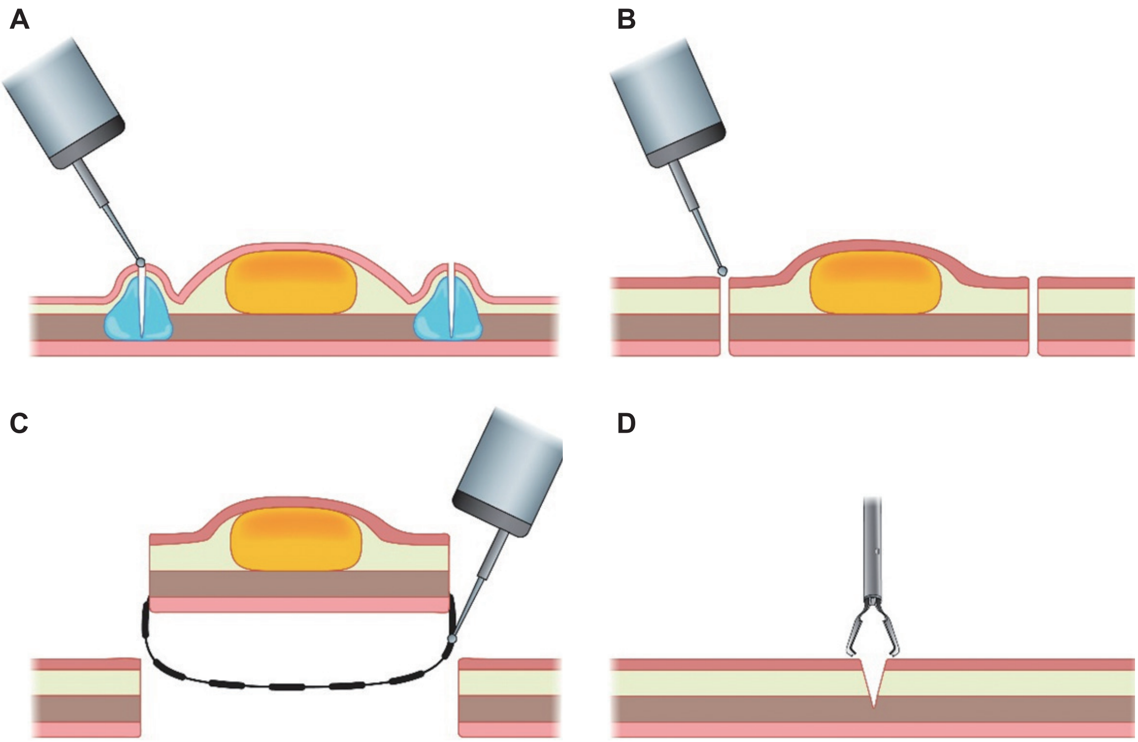

Fig. 3. Endoscopic full-thickness resection. Marking, injection, and circumferential incision (A), incision (B), specimen resected with snare (C), and closure using endoscopic clips (D).

denal carcinoid tumors (Fig. 3).[12] EFTR was devised to overcome the drawbacks of ESD for R0 resection and removal of MP lesions. Using this advanced technique, a dependable endoscopic suture device is crucial for suturing in open areas. The OverStitch system, a commercially available full-thickness suture endoscope, employs surgical technology sutures.[13] Another device is the over-the-scope clip system (OTSC®; Ovesco Endoscopy AG), an endoscopic clip device used for tissue closure.[14,15] A full-thickness resection device (FTRD) utilizing an OTSC system has recently been developed as a more advanced mechanism for unexposed EFTRs.[16]

Zhou et al.[5] documented 26 cases of EFTR in patients with gastric GISTs. All cases involved R0 resections, with an average tumor size of 28 mm (range, 12–45 mm). In all cases, an open full-thickness layer after resection was effectively sealed with an endoscopic clip. Guo et al.[17] documented 23 cases of EFTRs that were followed by endoscopic sutures using OTSCs. EFTR procedures were successful in all cases, with no delayed perforation during the 3-month follow-up. Tumor sizes averaged 12.1±4.7 mm, ranging from 6 to 20 mm. Histological reports showed one high-risk GIST (4%), 18 very low-risk GISTs (78%), and four leiomyomas (17%). Local peritonitis occurred in two cases (9%). Ye et al.[18] studied EFTR's safety and efficacy using clips and endoloops after removing SELs from the MP layer in 51 patients. EFTR was successfully performed in 98% of the patients, with an average procedure time of approximately 52 min. In a study of 62 patients, Lu et al.[19] compared the outcomes of three different EFTR methods. The endoscopic procedure duration was significantly reduced when using thread-with-clip and loop-assisted techniques compared with the traditional method. The mean lesion size was approximately 2 cm. Effective traction using these methods contributed to the successful execution of the EFTR. However, because these procedures require technical skill from endoscopists, they may be challenging to perform easily from a technical perspective.

Shichijo et al.[20] conducted a multicenter phase II study that demonstrated that EFTR is effective and safe for gastric submucosal tumors measuring 11–30 mm. In 46 patients, the complete ER rate was 100% with no need for surgical conversion. Most lesions were GISTs, and the number of adverse events was minimal. These findings suggest that EFTR is a promising therapeutic option.

Submucosal tunneling endoscopic resection

STER was initially used to treat SELs of the esophagus and gastric cardia (Fig. 4).[21-24] Compared to other endoscopic resection techniques, STER provides several advantages: it maintains mucosal integrity, accelerates wound healing, and reduces the risk of complications such as infection.[25-27] Several

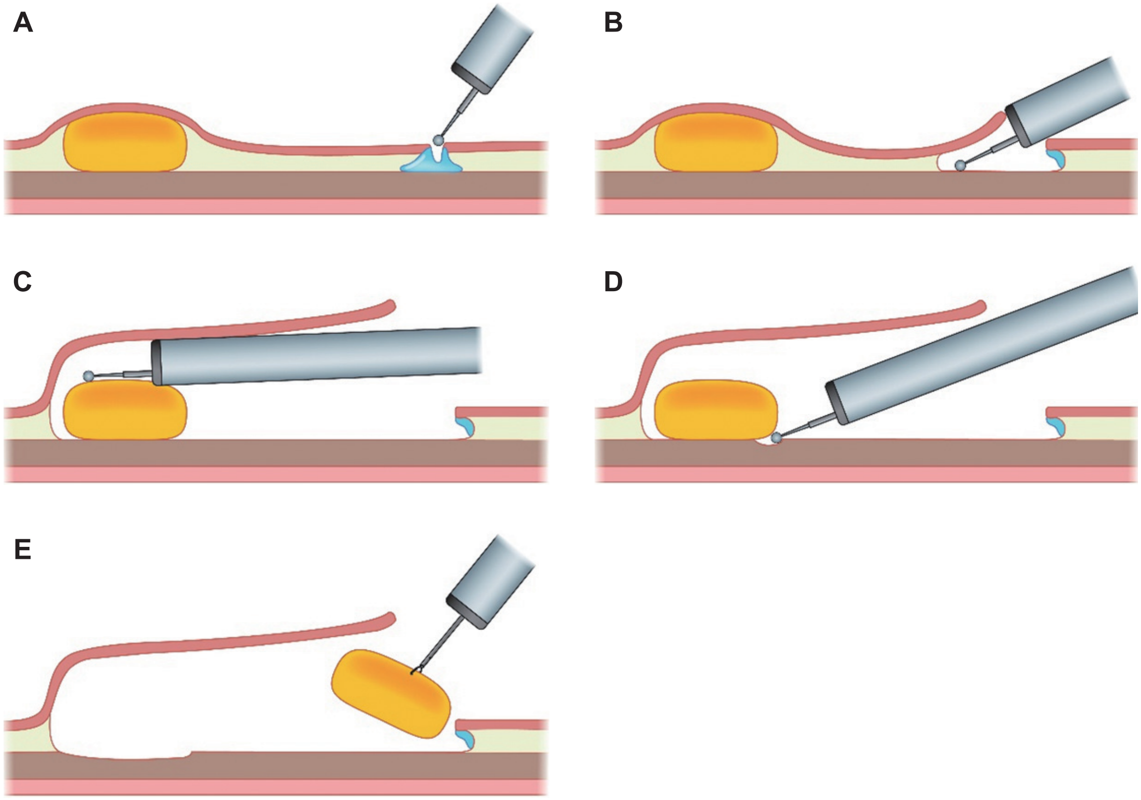

Fig. 4. Endoscopic submucosal tunneling resection. Injection (A), creation of the submucosal tunnel (B), continued tunneling (C), myotomy (D), removal with endoscopic forceps (E).

studies have demonstrated the effectiveness and safety of STER for treating gastric SELs. Tan et al.[27] compared STER with EFTR in their study. Both demonstrated similar safety and efficacy; however, EFTR required more endoscopic clips to close the stomach wall defect. Wang et al.[28] performed a one-tunnel STER to remove multiple SELs in 12 patients. The average procedure took 92.1±40.8 min, during which 30 SELs were fully resected. All lesions were successfully resected, with no recurrence observed over an average follow-up of 24.9±15.3 months. Nevertheless, STER has certain limitations, including difficulty in accessing lesions located in the upper great curvature and fundus and challenges associated with removing tumors exceeding the esophageal diameter.[23,27]

Laparoscopic and endoscopic cooperative surgery

The concept of LECS originated in 2008 after the development of ESD. This approach involves close teamwork between endoscopists and surgeons in the same operating room to treat a single patient. In Japan, from October 2007 to December 2011, 126 patients with gastric SELs were treated with LECS at eight different institutions.[29] The average operation time for LECS was 190.2 min (standard deviation [SD] 66.8 min), with an estimated blood loss of 15.1 mL (SD 38.6 mL). LECS has demonstrated safety and practicality in removing gastric SELs, characterized by a reasonable duration, minimal bleeding, and an acceptable rate of complications.[30,31] Classical LECS involves creating an iatrogenic perforation during the procedure, which increases the risk of tumor cell seeding in the abdominal cavity. To address this issue, several non-exposure techniques have been developed as alternatives to LECS. These include methods such as the combination of laparoscopic and endoscopic approaches for neoplasia with a non-exposure technique (CLEAN-NET), non-exposure endoscopic wall inversion surgery (NEWS), and non-exposure simple suturing EFTR (NESS-EFTR)/closed LECS.[32-35] These techniques prevent accidental perforation of the gastric wall, making them ideal for submucosal tumors without mucosal ulceration. Closed LECS, a new variation of LECS, involves inverting the tissue and performing seromuscular dissection without exposing the gastric lumen. These methods are effective for tumors up to 3 cm in size and offer similar oncological safety with a lower risk of contamination, making them safer options than traditional LECS for certain lesions.

EFFICACY OF ENDOSCOPIC RESECTION FOR GASTRIC SELs

Current guidelines suggest laparoscopic resection for gas-

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tric GISTs, with a long-term recurrence rate of 0%–8% (follow-up, 35–75 months).[36-43] However, laparoscopic resection carries the risk of injuring the pseudocapsule, and using a laparoscopic port for tumor removal raises the risk of peritoneal seeding. Surgery becomes more challenging when the GIST is situated in the prepyloric area, esophagogastric junction, or cardia of the stomach.[44]

Joo et al.[4] assessed the effectiveness and safety of endoscopic resection for GISTs, and compared their findings with those of surgical resection outcomes. The authors studied 130 patients with upper gastrointestinal lesions and tracked their outcomes. Tumor sizes were smaller in the endoscopic group (2.3 cm vs. 5.1 cm, $p<0.001$). The procedure duration and length of hospital stay were shorter in the endoscopic group. The R0 resection rate was higher in surgical cases (25.6% vs. 85.0%, $p=0.001$). Despite this, recurrence rates over 45.5 months were similar (2.2% vs. 5.0%, $p=0.586$). Shen et al.[45] compared endoscopic and surgical resection in 54 patients with gastric GISTs (<2 cm). Patients who underwent endoscopic resection had shorter hospital stays than those who underwent surgery ($p<0.001$). Blood loss, nasogastric tube insertion time, and procedure durations were significantly higher in the surgery group ($p<0.001$). Over 34.5 months of follow-up, one high-risk patient in each group experienced recurrence. A meta-analysis of five studies compared endoscopic and surgical resection for gastric GISTs.[46] The average tumor size ranged from 1.1 cm to 3.8 cm, with the endoscopic resection group having smaller mean sizes than the surgical resection group ($p=0.03$). There were no significant differences between the two groups concerning intraoperative bleeding, length of hospital stay, postoperative complications, or recurrence rates. Nonetheless, endoscopic resection procedures took significantly less time than surgical resections ($p<0.001$).

FUTURE DIRECTIONS FOR ENDOSCOPIC RESECTION

Future advancements in endoscopic resection are expected across all major techniques. For ESD, improvements in traction-assisted methods, hybrid knives, and AI-guided delineation of the submucosal planes may enhance the efficiency and lower perforation risks. EBL is likely to evolve with more precise ligation devices and advanced imaging tools to better assess the depth and completeness of resection in small SELs. STER may benefit from improved tunneling instruments and real-time navigation systems, potentially expanding its use beyond the esophagus and cardia of the stomach. In EFTR, ongoing refinement of endoscopic suturing and full-thickness closure devices is crucial for safety, particularly for lesions near critical structures. For LECS, particularly non-exposure variants like NEWS and CLEAN-NET, hybrid techniques combining robotic assistance and endoluminal access have been explored to reduce contamination risks while enabling the resection of larger or more complex lesions. Overall, these innovations aim to improve procedural outcomes, expand indications, and increase patient safety in the minimally invasive management of gastrointestinal SELs.

In addition, a reliable endoscopic suturing device is crucial for safe removal of SELs from the MP layer using procedures such as EFTR. Significant advances in endoscopic suturing technology could greatly enhance techniques for resecting SELs. Currently, commercial endoscopic tools include only the overstitch system that requires a 2-channel endoscope and is unsuitable for general endoscopy. Another available device is the OTSC, a clip-type device compatible with standard 1-channel endoscopes. The OTSC system can be mounted at the end of the endoscope and used for various applications, such as gastrointestinal bleeding, perforations, fistulas, and anastomotic leakage.[47,48] It can also be used for endoscopic closure of an artificial perforation following endoscopic procedures.[49] The OTSC system is designed to offer more advanced endoscopic closure than traditional clips. However, its effectiveness could be limited by the size of the gastrointestinal wall defect, and its high cost remains a concern.[50] Goto et al.[51] presented an endoscopic suture method. This technique employs a nonabsorbable suture threaded through a curved needle, using a through-the-scope needle fixation device. It mimics the hand-suturing method performed by surgeons. This method is suitable for the continuous linear suturing of gastrointestinal mucosal defects. Successful implementation depends on the skills of experienced endoscopists and assistants. Recently, Mori et al.[52] introduced a double-armed bar suturing system (DBSS; Zeon Medical Co.) designed for a full-thickness suture mechanism. It can be used with a standard 1-channel endoscope and allows sealing of the opened gastric wall with a strength comparable to that of a hand-sewn stitch. The DBSS can easily be attached to the end of a regular endoscope as a hood. Several endoscopic suturing devices have been developed for this purpose. Although various endoscopic devices, such as OverStitch, OTSC, FTRD, and DBSS, have shown promising results in Western studies, their clinical use in Korea remains limited. Currently, the OTSC is the only widely available and approved full-thickness closure system in Korea. The OverStitch and FTRD systems have not yet received domestic regulatory approval or are not routinely accessible owing to their high costs or lack of insurance coverage. Therefore, clinicians in Korea often rely on alternative closure methods, including endoloops, clips, and laparoscopic assistance when performing

EFTR or complex resections.

CONCLUSION

Recent progress in understanding the behavior of SELs and improvements in endoscopic tools have enabled precise and informative diagnoses. Furthermore, advancements in endoscopic techniques have supported invasive surgical procedures, enabling efficient management of SELs. As some SELs carry a potential risk of malignancy, minimally invasive endoscopic resection may be preferable over ongoing surveillance. Although the endoscopic approach to SELs is still debated, the ongoing development of devices and techniques suggests that more sophisticated and effective treatments will be available in the near future. A multidisciplinary approach is essential for managing SELs, minimizing complications, and enhancing outcomes. With more research and long-term data, the effectiveness of endoscopic treatment for SELs will become increasingly evident.

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