—Review—

Cutting-Edge Technologies for Gastrointestinal Therapeutic Endoscopy

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With advancements in the development of flexible endoscopes and endoscopic devices and the increased demand for minimally invasive treatments, the indications of therapeutic endoscopy have been expanded. Methods of endoscopic treatment used for tissue removal, hemostasis, and dilatation are as follows. Endoscopic submucosal dissection (ESD) is considered the gold standard curative method for removal of gastrointestinal node-negative neoplasms, regardless of their size or the presence of ulcer formation. Laparoscopic endoscopic cooperative surgery (LECS), which incorporates ESD, was introduced for removal of lesions in deeper layers. Another technique is endoscopic full-thickness resection, which is challenging without the assistance of laparoscopy. In terms of hemostasis, management of iatrogenic bleeding after endoscopic treatment is an important issue. Shielding methods and suturing techniques have been introduced for large mucosal defects after ESD, and their efficacy has been investigated clinically. Peroral endoscopic myotomy (POEM) is a new alternative surgical approach for minimally invasive treatment of esophageal achalasia. Furthermore, endoscopic fundoplication after POEM was devised to prevent post-POEM gastroesophageal reflux disease. Many endoscopic treatments, including ESD, LECS, and POEM, have been introduced in Japan. With the aging of the population, more attention will be directed toward therapeutic endoscopy for elderly patients, because it is less invasive. Development of endoscopic treatments with expanded indications is expected.

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Key words: therapeutic endoscopy, endoscopic submucosal dissection, endoscopic full-thickness resection, peroral endoscopic myotomy

Introduction

Endoscopic treatment was introduced in Japan in the 1960s; until then, flexible endoscopy was simply used as a diagnostic tool. As the endoscope developed along with accessories, various endoscopic treatment modalities have emerged. As compared with conventional surgical approaches, endoscopic treatments have the key advantage of being minimally invasive. Most endoscopic treatments require only intravenous sedation, which results in fast recovery postoperatively and no general anesthesia-related risks. Additionally, to reach a target lesion, they use natural orifices, such as the mouth or anus; thus, surgical scars, postoperative somatic pain, and cosmetic defects are avoided. Moreover, doctors and patients broadly acknowledge the merits of endoscopic procedures; thus, endoscopic treatments are preferred over open surgery if similar outcomes can be obtained in terms of technical success and outcomes.

Therapeutic endoscopy is used for several purposes (**Table 1**), including tissue removal, hemostasis, and dilatation. In this narrative review, we summarize the currently available procedures and introduce the latest advances in this field.

Tissue Removal

In 1968, endoscopic polypectomy was the first endoscopic treatment performed and reported in Japan[1] and is still recommended for removing pedunculated polyps, regardless of anatomical location. Mechanical polypectomy without electrocautery, known as cold snare/for-

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Table 1 Established endoscopic treatments

Aims and procedures	Organs	Major indication
Tissue removal		
Endoscopic polypectomy	Whole tract	Benign polyp, Neoplasia
Endoscopic mucosal resection (EMR)	Whole tract	Benign polyp, Neoplasia
Endoscopic submucosal dissection (ESD)	Esophagus, Stomach, Duodenum, Colorectum	Cancer
Laparoscopic endoscopic cooperative surgery (LECS)	Stomach	Submucosal tumor
Hemostasis		
Endoscopic hemostasis	Whole tract	Bleeding
Algon plasma coagulation (APC)	Whole tract	Bleeding
Endoscopic variceal ligation (EVL)	Esophagus, Stomach	Varices
Endoscopic injection sclerotherapy (EIS)	Esophagus, Stomach	Varices
Endoscopic band ligation (EBL)	Colon	Diverticular bleeding
Dilatation		
Endoscopic balloon dilatation (EBD)	Whole tract	Benign stricture
Endoscopic stent placement	Esophagus, Colon	Malignant stricture
Peroral endoscopic myotomy (POEM)	Esophagus	Achalasia
Others		
Endoscopic foreign body removal	Whole tract	Accidental ingestion
Percutaneous endoscopic gastrostomy (PEG)	Stomach	Oral feeding difficulty
Photodynamic therapy (PDT)	Esophagus	Cancer
Endoscopic intragastric balloon placement[a)]	Stomach	Obesity
Endoscopic gastroplasty[a)]	Stomach	Obesity
Radiofrequency ablation (RFA)[a)]	Esophagus	Barrett's esophagus

a) Not currently approved in Japan

ceps polypectomy, is widely used for removal of colorectal polyps less than 1 cm[2,3].

In the 1980s, endoscopic mucosal resection (EMR) was used to remove large polyps. The accompanying devices used in EMR techniques are grasping forceps to lift the lesion[4,5]; a transparent hood and a snare to aspirate the lesion; and a rubber band to create a pseudopolyp[1]. However, EMR techniques are limited in resection size by the use of a snare; thus, complete en bloc resection is challenging and the probability of local recurrence in cases of piecemeal resection is high[6]. Furthermore, lesions with submucosal fibrosis will be incompletely removed because the snare slips because of the presence of submucosal hard tissue under the lesion.

In the late 1990s, endoscopic submucosal dissection (ESD) resolved the resection size limitation of EMR by using a circumferential mucosal incision and subsequent submucosal dissection below the lesion with a specially designed electrocautery knife[7–9]. This technique allowed the removal of larger lesions, regardless of the presence of submucosal fibrosis, and is now used as a minimally invasive endoluminal surgery for treating early cancers with negligible risk of lymph node metastasis. This technique was first used to treat gastric lesions, and, later, esophageal and colorectal lesions. However, using ESD for duodenal lesions is still challenging because of the poor maneuverability of the endoscope and difficulty in managing adverse events[10]. Moreover, the surgical approach is invasive.

The ESD technique has been used for local resection along with laparoscopy. Laparoscopic endoscopic cooperative surgery (LECS) was developed to locally remove gastric submucosal tumors[11,12]. In this technique, the resection area is marked endoscopically by a circumferential mucosal incision, followed by full-thickness resection endoscopically or laparoscopically through intentional perforation, after which the wall defect is firmly closed laparoscopically. The procedure time is approximately 3 hours in ordinary LECS for submucosal tumors of 2 to 5 cm[12]. The endoscopic approach compensates for the weakness of invisible demarcation from the outside, whereas the laparoscopic approach allows for closure of the defect from the inside. LECS is indicated for gastric submucosal tumors, such as gastrointestinal stromal tumors, in which local resection is acceptable because of the low risk of lymph node metastasis. Furthermore, nonexposure techniques[13–15], advanced LECS methods, in combination with sentinel node navigation surgery[16,17], are used to treat node-positive early gastric cancer.

Purely endoscopic transoral retrieval and removal of

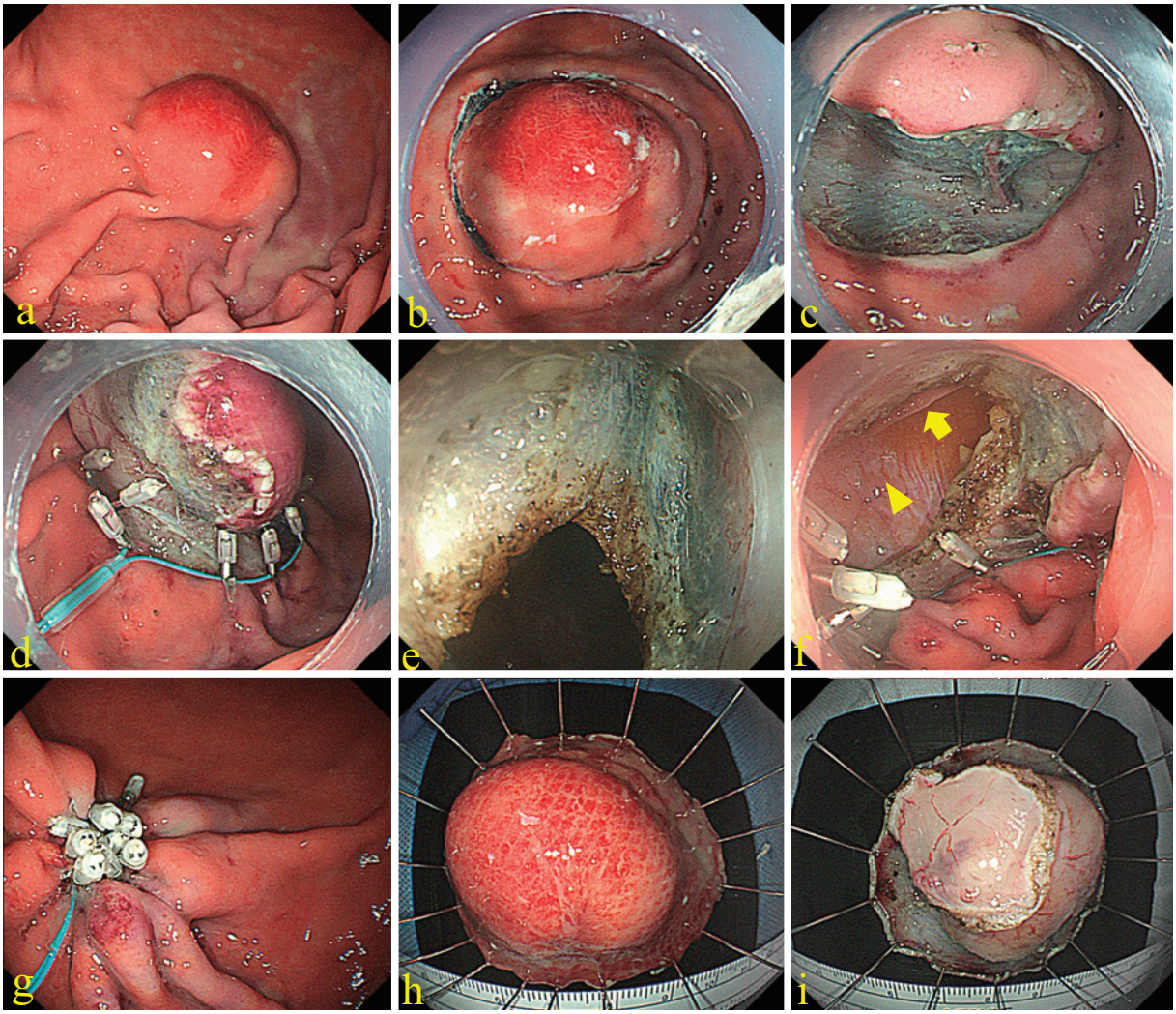

Fig. 1 Simulated EFTR with laparoscopic assistance. (a) A submucosal tumor is located at the greater curvature on the lower part of the gastric body. (b) A circumferential mucosal incision is made. (c) Submucosal dissection is performed to the edge of the tumor. (d) A detachable snare is placed on the mucosal rim with clips and temporarily released. (e) A circumferential seromuscular incision is performed under the traction of the tumor. (f) The lesion is removed and retrieved perorally. A full-layered defect is created (arrow, edge of the liver; arrowhead, parietal peritoneum). (g) The defect is closed in a purse-string manner by closing the snare. (h) The mucosal side of the resected lesion. (i) The serosal side. Resection was complete.

gastric submucosal tumors (less than 3 cm) can be challenging. Endoscopic full-thickness resection (EFTR) was introduced in China[18–20] and was recently performed in Japan[21,22]. All steps in the EFTR procedure, such as circumferential mucosal incision, circumferential seromuscular incision after intentional perforation, and defect closure, are done endoscopically. In this procedure, small submucosal tumors can be removed in about 1 hour[20,21]. With regard to target lesion accessibility, using laparoscopy in the LECS approach can be difficult for some lesion sites, for example, the posterior wall of the upper stomach. Therefore, EFTR may be the most suitable technique for these cases. After approval was obtained for this technique as an advanced medical treatment in Japan, clinical trials of its efficacy are underway at leading hospitals.

Figure 1 illustrates simulated EFTR with laparoscopic assistance. Circumferential mucosal incision is easily performed by using the ESD technique. Seromuscular incision requires tips because the working space collapses after intentional perforation, because of leakage of the air inside the stomach, which results in poor endoscopic visualization. Under these conditions, suitable lesion traction is necessary. Therefore, a clip-with-line method[23] and other similar techniques were proposed, where a clip with a long line (surgical suture, dental floss, etc.) tied to a blade was attached to the lesion and lifted in the oral direction by pulling the line for traction of the seromuscular layer, which provides a good view of the lesion in

the stomach.

In EFTR, several disadvantages attributable to the laparoscopy-free situation should be considered. Gastric juice is more likely to spill and pool in the abdominal space than in LECS. Specifically, nonexposure LECS, which does not open the digestive tract to the abdominal cavity, is less likely than EFTR to cause peritonitis due to intraperitoneal contamination of digestive juice. Control of intraabdominal pressure may be difficult by means of simple puncture of the abdominal wall, without an indicator to monitor pressure, because carbon dioxide gas must be continuously supplied through the endoscope to maintain good endoscopic visualization. The most important and controversial issue is endoscopic closure of full-thickness defects. At present, purse-string closure with a detachable snare and clips[24] is used. A detachable snare, which is used for performing prophylactic hemostasis before removal of large pedunculated polyps, is placed on the mucosal rims of the defect with several clips. By tightening the snare, the defect is closed in a purse-string fashion. In this technique, only the mucosal layer is closed; seromuscular layers are not sutured, which could increase the risk of anastomotic leakage. Although previous studies of a large number of clinical cases in China reported no incidence of leakage associated with these techniques, a fasting period of 3 days or longer is required in order to stabilize the defect site histologically. Development of a secure, reliable closure method is warranted (hopefully, a full-thickness closure technique).

Hemostasis

Therapeutic endoscopy is of great importance in emergency settings. Endoscopic hemostasis for gastrointestinal bleeding is likely the most familiar endoscopic procedure in emergency medicine[25]. Hemostatic techniques include clips (including the over-the-scope clip), electrocautery forceps, ethanol injection, and hypersaline plus epinephrine injection for arterial bleeding from ulcers; argon plasma coagulation for oozing from vascular ectasia, angiodysplasia, or a cancerous surface; endoscopic variceal ligation (EVL) for esophageal/rectal variceal rupture; endoscopic injection sclerotherapy for gastric variceal rupture; and endoscopic band ligation (similar to EVL) for colonic diverticular bleeding. Hemospray, a hemostatic powder sprayed onto bleeding sites without contact, is useful in managing different types of bleeding[26]; however, it is not commonly used in Japan. Currently, these techniques are chosen on the basis of the bleeding situation and the endoscopist's preference in clinical settings.

With the development of endoscopic treatment techniques, the incidence of postoperative gastrointestinal bleeding has increased. Post-ESD gastric bleeding is the most common and occurs in approximately 5% and 20% to 30% of low-risk and high-risk patients taking antithrombotic agents, respectively[27,28]. With the increase in the elderly population, the number of patients using antithrombotic agents is increasing. Therefore, prevention of post-ESD bleeding is an urgent issue.

Several studies have reported attempts to shield mucosal defects to prevent delayed bleeding. Covering the defect with a polyglycolic acid sheet, generally used for preventing intraperitoneal adherence after surgery, may be helpful to prevent delayed bleeding[29]; however, clinical studies have reported inconsistent outcomes[30]. Moreover, mucosal closure with clips[31] and purse-string closure with a detachable snare and clips[32] are sometimes used; however, with these methods, complete closure of a large ESD defect is challenging, and if successful, the defect may not remain closed.

For tight, secure closure of mucosal defects, endoscopic suturing was introduced. In the 2000s, the Overstitch™ suturing system (Apollo Endosurgery, Inc., Austin, TX, USA) was devised to close an intentionally created transluminal hole in natural orifice transluminal endoscopic surgery (NOTES), which included challenging therapeutic endoscopy procedures, for example, transgastric endoscopic appendectomy and transvaginal endoscopic cholecystectomy. In the 2010s, the preference for using NOTES declined because it was an aggressive procedure and was not clinically needed; however, Overstitch™ survived as a spin-off device of NOTES for intraluminal suture of gastrointestinal tissue. Endoscopic suturing of mucosal defects after ESD using this device is useful in preventing post-ESD bleeding[33]. Use of this suturing device seems promising in the field of therapeutic endoscopy because it is easy to use, requires only a short suturing time (13 minutes for 1.6 stitches[33]), and provides secure, long-lasting, full-thickness closure. However, it is costly and not available worldwide.

In Japan, an endoscopic hand-suturing (EHS) technique was devised in 2012[34]. In this technique, the mucosal layer is continuously sutured in a manner similar to surgical suturing (**Fig. 2**). Furthermore, an absorbable barbed suture is used, which eliminates knot tying. Using a through-the-scope flexible needle holder (Olympus Co., Ltd., Tokyo, Japan), the endoscopist can firmly grasp and smoothly rotate the needle. After confirming the feasibility and safety of this technique in ex vivo[34] and in

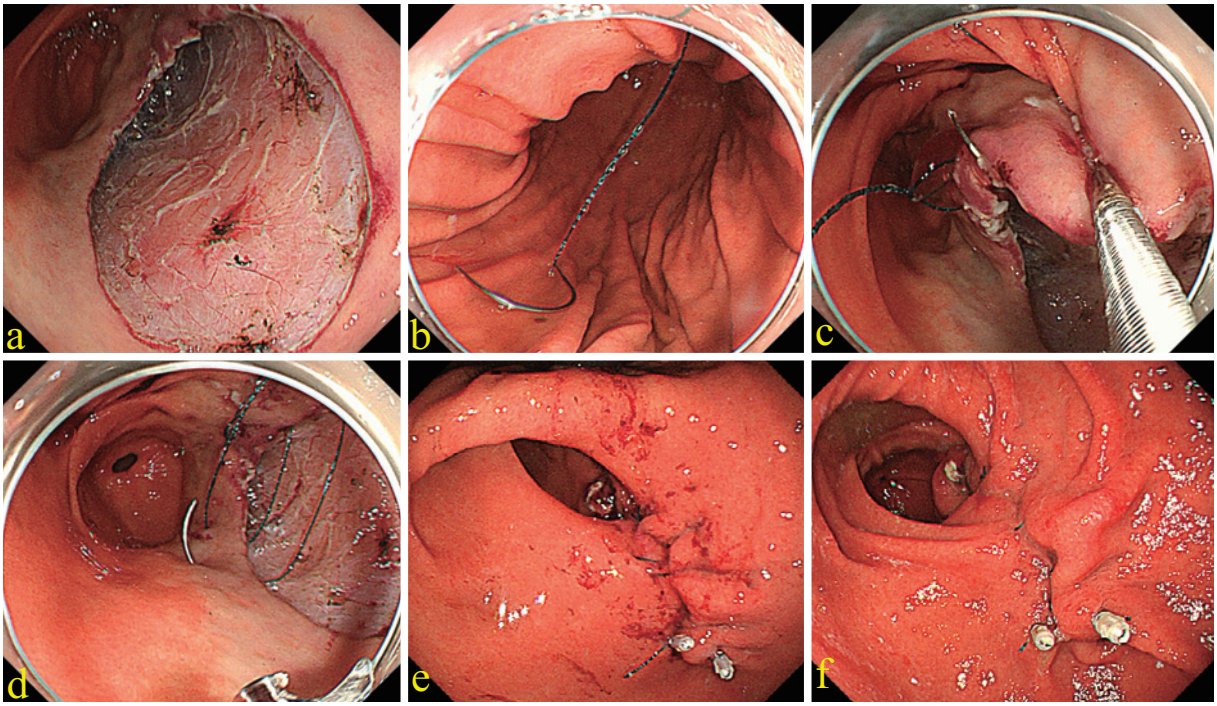

Fig. 2 Endoscopic hand-suturing for a mucosal defect after gastric endoscopic submucosal dissection. (a) A mucosal defect is located on the posterior wall of the gastric antrum. (b) A barbed suture is grasped with the flexible needle holder and delivered to the stomach through an overtube. (c) Continuous suturing is initiated at the distal side of the defect. (d) Optimal lengths of the bite and pitch are needed for long-lasting closure. (e) The defect is completely closed. (f) The suturing site at 2 months postoperatively. The mucosal defect remains closed.

vivo porcine models[35], a multicenter pilot study of 30 clinical cases was conducted[36]. The EHS technique was successfully implemented in 97% of the patients, the defect closure was maintained in 83%, and no delayed bleeding occurred in patients with sustained closure (excluding a remnant stomach case), regardless of antithrombotic agent use, although the procedure time was long (50 minutes for 8.0 stitches). EHS is expected to decrease the risk of delayed bleeding after gastric ESD, even in high-risk patients. Further trials of the usefulness of EHS and expansion of indications for these techniques are required.

Dilatation

Endoscopy can less invasively manage benign or malignant strictures of the gastrointestinal tract. Endoscopic balloon dilatation (EBD) is a widely used technique for benign strictures caused by esophageal webs, primary achalasia, anastomosis, ESD, and inflammatory bowel diseases. EBD is technically less demanding, safe, and easily accessible to endoscopists but disadvantageous in the long term. In particular, for treating esophageal benign strictures, endoscopic radial incision and cutting method[37,38] may be a good alternative to EBD. In this technique, an electrocautery needle knife is used to create several radial gutters on a narrow part of the lumen, after which fibrotic tissue between the gutters is removed. In contrast, endoscopic stent placement[39] is used mainly for management of malignant strictures, particularly when attempting to maintain patient quality of life. To prevent adverse events such as perforation, migration, and kinking, various types of stents are being developed and improved.

For esophageal achalasia, a novel endoscopic treatment was introduced in 2010, known as peroral endoscopic myotomy (POEM)[40]. In this procedure, the incision of the inner circular muscle at the esophagogastric junction is performed endoscopically, as an alternative approach to surgery (**Fig. 3**). After the submucosal injection and mucosal incision in the oral direction of the lower esophageal sphincter (LES), a submucosal tunnel is created toward the stomach. Then, a longitudinal incision of the inner circular layer 2 cm above to 2 cm below the LES is made. The entry site of the submucosal tunnel is then closed with clips. The mean procedure time was 88 minutes in 27 consecutive cases at our institution, which is comparable to that of laparoscopic Heller myotomy. POEM has permeated worldwide because of its accessibility and limited invasiveness. In a meta-analysis of clinical outcomes of POEM[41], the 1-year response rate (ie,

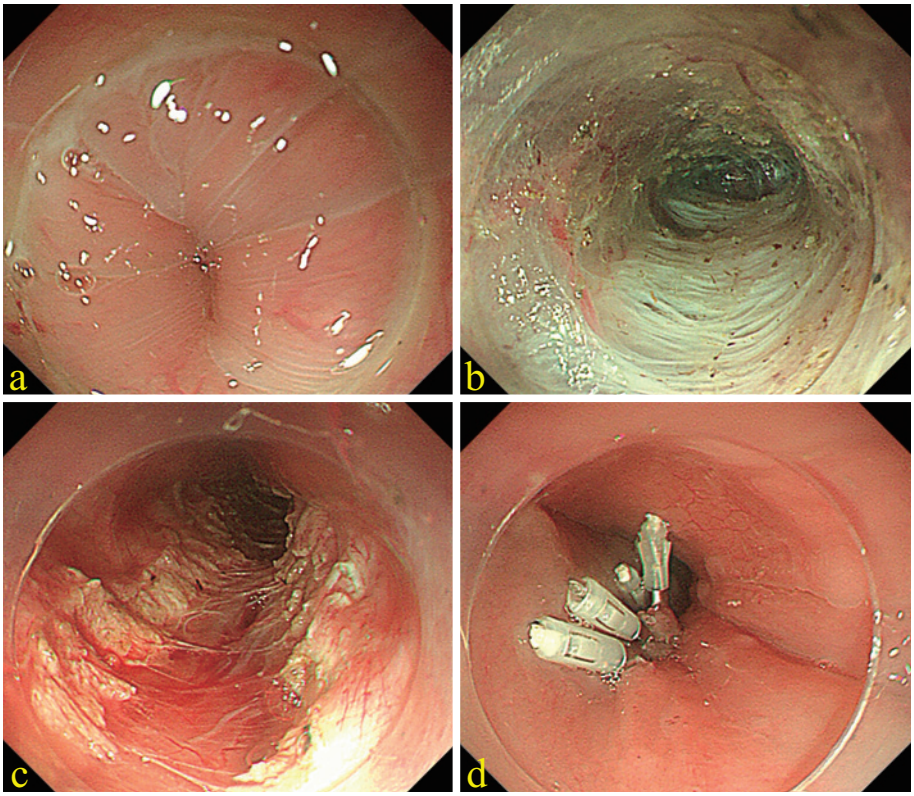

Fig. 3 Peroral endoscopic myotomy. (a) Primary esophageal achalasia shows dysfunction of relaxation at the lower esophageal sphincter ("esophageal rosette" sign). (b) A submucosal tunnel is created over the stricture area. (c) Incision of the inner muscular layer is performed. (d) The procedure is terminated by closing the entry side of the submucosal tunnel with clips.

a decrease in Eckardt score to 3 or lower) was 98%. The perioperative adverse events were mucosal damage in 4.8% of cases, mucosal perforation in 0.2%, massive bleeding in 0.2%, and subcutaneous emphysema in 7.5%. The late-phase adverse events were symptomatic gastroesophageal reflux disease in 8.5% of cases and reflux esophagitis in 13%.

Recently, to prevent postoperative reflux esophagitis, Inoue and colleagues, who invented the POEM technique, introduced endoscopic fundoplication after POEM[42]. They wrapped the esophagogastric junction with the gastric fundus by retracting the anterior wall with a detachable snare and clips[42] or the EHS technique[43]. In this procedure, the tip of the endoscope is advanced through the submucosal tunnel to the peritoneal space, to hook and pull the gastric fundus, during which the endoscope is completely outside the lumen. Therefore, this technique can be considered as successful as NOTES clinically. Although it is unclear whether this procedure should be mandatory for all POEM cases, endoscopic fundoplication is challenging and interesting and may allow for operations outside the lumen as part of a revival of NOTES.

Conclusions

Endoscopy has been used as a treatment tool since the 1960s. Over the years, indications for endoscopic treatment have gradually expanded and now include removal of targeted lesions, from tiny polyps to large and deep neoplasms; management of various bleeding types, from peptic ulcers or varices to iatrogenic bleeding; dilatation of benign and malignant strictures; and even motor dysfunction diseases. Many endoscopic treatments have been introduced and developed in Japan, owing to the determined efforts of therapeutic endoscopists and improvements in endoscopic devices. Endoscopic treatment has a great advantage over other surgical approaches-it is less invasive. Therefore, the need for therapeutic endoscopy will grow. Patients who prefer minimally invasive treatments for gastrointestinal disease will benefit from further developments in this field.

Conflict of Interest: The authors declare no conflicts of interest.

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