



# Breaking the Barrier in Endoscopy

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## Abstract

### Keywords

- ▶ deep enteroscopy
- ▶ motorized spiral enteroscopy
- ▶ cholangioscopy
- ▶ pancreatoscopy
- ▶ third-space endoscopy
- ▶ peroral endoscopic myotomy

In this narrative review, invited by the Editors of the Journal of Digestive Endoscopy, we summarize recent advances in the field of gastrointestinal endoscopy with regard to reaching the earlier inaccessible areas in the gut by newer methods and technology. This article primarily discusses recent advances in the past few years in the following headings: (1) reaching redundant small bowel via enteroscopy (primarily motorized spiral enteroscopy), (2) reaching the thin pancreaticobiliary ducts via cholangioscopy and pancreatoscopy, (3) going out of the gut wall: third-space endoscopy (primarily peroral endoscopic myotomy: POEM). A thorough literature review was performed on each topic describing how the advances were evolving.

## Introduction

Innovations in the field of gastrointestinal (GI) endoscopy over the last two decades have made it possible to reach the earlier inaccessible areas in the GI tract. Methods of deep small bowel endoscopy by balloon-assisted enteroscopy were far from ideal due to sub-optimal pan-enteroscopy rates and prolonged procedure time. Difficult biliary/pancreatic stones and indeterminate strictures were often subjected to surgical therapy. GI diseases such as achalasia cardia and refractory gastroparesis often required surgical myotomy until submucosal space was recognized as a potential operative field as third-space endoscopy evolved. All these potential barriers in interventional endoscopy have been circumvented by newer technologies such as motorized spiral enteroscopy, cholangio-pancreatoscopy, and third-space endoscopy. These innovations are propelling the field of advanced GI endoscopy forward. We describe our experience with regard to the technological

evolutions and landmarks we observed over the last two decades.

## Venturing Deep into Small Bowel

### Evolution of Small Bowel Enteroscopy

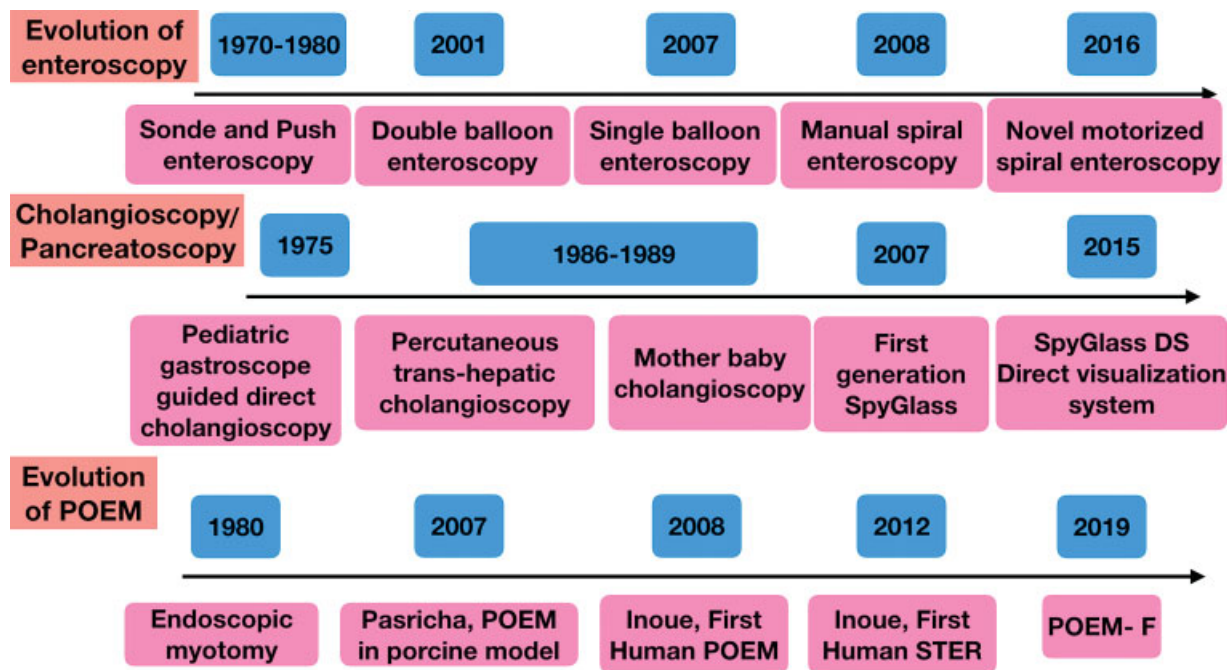
The first breakthrough in deep enteroscopy began with the invention of the double-balloon enteroscope (DBE) (Fujifilm, Tokyo, Japan) way back in 2001 in Japan by Hironori Yamamoto.<sup>1</sup> This was followed by the introduction of single-balloon enteroscopy (SBE) (Olympus Medical Systems Corp, Tokyo) in 2007.<sup>2</sup> Compared with DBE, SBE has only one balloon located at the tip of the over-tube and uses the hooked tip of the endoscope to fix the intestine. SBE is non-inferior to DBE with regard to the depth of insertion, diagnostic yield, and rate of complications with shorter preparation and investigation time although panenteroscopy rates are better with DBE.<sup>3</sup> Principles of balloon-

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**Fig. 1** “Breaking the barrier in endoscopy”: evolution of deep enteroscopy, cholangiopancreatoscopy, and third-space endoscopy (peroral endoscopic myotomy: POEM); POEM-F: peroral endoscopic myotomy with fundoplication.

assisted enteroscopy (BAE) depend upon the serial “push and pull maneuver” to pleat the small intestine. A large study from India including 106 patients showed diagnostic yields of 55%, 60%, and 65% for chronic diarrhea, obscure GI bleed, and chronic abdominal pain, respectively, with a 25% panenteroscopy rate. Therapeutic interventions were performed in 21% via SBE, which included argon plasma coagulation (APC), polypectomy, stricture dilatation, foreign body extraction, and hemoclips for jejunal Dieulafoy’s lesion (►Fig. 1).<sup>4</sup>

After SBE, manual spiral enteroscopy (SE) (Spirus Medical, Stoughton, Mass, USA) was introduced in 2008.<sup>5</sup> SE depends on the principle of “rotation” rather than “push and pull.” The spiral overtube was 118 cm long, which was compatible with standard single and double-balloon enteroscope (200 cm). This left only 90 to 95 cm of effective length and only 30 to 35 cm of functional scope beyond the ligament of Treitz to perform small bowel pleating, making it difficult to perform pan-enteroscopy even by the most experienced endoscopist. Also, the requirement for manual spiral rotation caused significant wear and tear on the endoscopist. SE has a similar diagnostic and therapeutic yield, similar depth of insertion but importantly shorter procedure time compared with BAE based on a systematic review and meta-analysis.<sup>6</sup> In a series of 11 cases of SE reported from India, the mean procedure time was 27.8 minutes (range: 20–32 minutes) (considerably lower than BAE) with an average depth of insertion of 249 cm (120–400 cm). No major complications were noted.<sup>7</sup>

#### Novel Motorized Spiral Enteroscopy

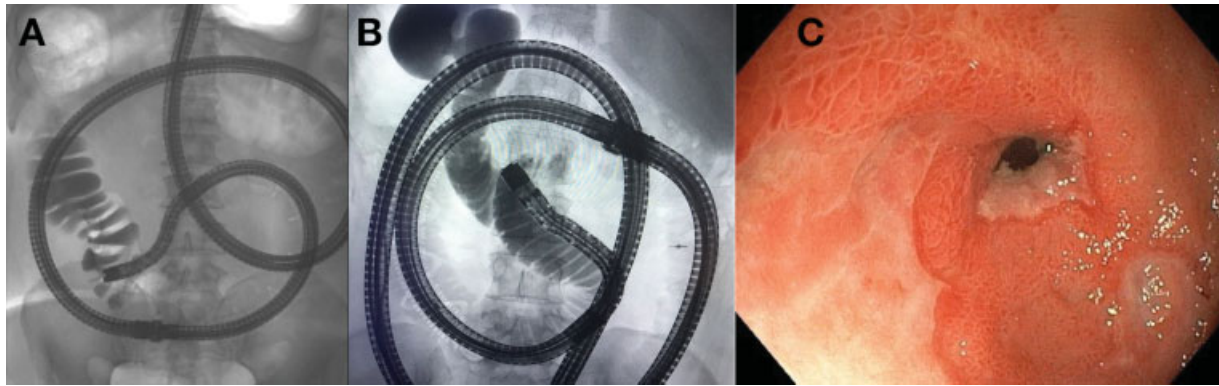
NMSE has addressed prior technical challenges in SE. It uses a longer enteroscope (working length 168 cm) with a short spiral over-tube (24 cm), which increases the likelihood of

pan-enteroscopy. An integrated water jet system and a larger working channel diameter (3.2 mm) allow for better therapeutic endoscopy.<sup>8</sup> A user-controlled spiral motor unit allows for a single operator to perform the procedure in an even faster and simplified manner. In a prospective clinical feasibility study of 140 procedures performed in two centers; the technical success, diagnostic yield, median depth of insertion, median insertion time, antegrade pan-enteroscopy rate, and major adverse events were 97%, 74.2%, 450 cm, 25 minutes, 10.6% and 1.5% respectively.<sup>9</sup> Total enteroscopy rate was reported to be 70% (in 53.4% pan-enteroscopy was achieved by bidirectional approach and in 16.6% cases by only antegrade approach).<sup>10</sup> Compared with western studies, the first real-world data from India on diagnostic yield and therapeutic impact of NMSE showed pan-enteroscopy rate was 60.6% of which 31.1% was noted in antegrade and 29.5% in bidirectional enteroscopy. Technical success and diagnostic yields were 93.4% and 65.5%, respectively. Also, 23% of patients underwent therapeutic spiral enteroscopy. No serious adverse events were reported. The major advantages of NMSE are shorter procedure time, single-operator use, higher pan-enteroscopy rates, and better provision of therapeutic small bowel endoscopy.<sup>8</sup> NMSE-guided removal of the impacted video capsule endoscope in distal ileum in a case of multifocal stricturing Crohn’s disease after balloon dilation of strictures has been reported.<sup>11</sup> This has the potential to revolutionize the management of small bowel disorders (►Fig. 2).

#### Exploring the Ducts

##### Evolution of Cholangioscopy and Pancreatoscopy

Endoscopic retrograde cholangiopancreatography (ERCP) is the main diagnostic and therapeutic modality for biliary



**Fig. 2** Novel motorized spiral enteroscopy (NMSE). (A) Antegrade pan-enteroscopy with NMSE: contrast injection showing opacification of the cecum, (B) Retrograde pan-enteroscopy with NMSE: contrast injection showing opacification of duodenal bulb, (C) Circumferential non-passable ulcerated stricture in mid ileum seen via antegrade route.

tract disorders that use fluoroscopy. However, ERCP has limitations in various biliary tract disorders such as stricture, tumor, cyst, and filling defects that may warrant direct visualization of the biliary tract. Differentiating benign and malignant biliary disease with brush cytology and biliary biopsy is suboptimal. Also, 5 to 10% of biliary stones may not be amenable to ERCP, endoscopic papillary balloon dilation (EPBD), and even mechanical lithotripsy.<sup>12</sup> To overcome the limitations, per-oral cholangioscopy was first performed in 1975. Since then, there are serial advancements in methods, accessories, and techniques the last few decades (→ Fig. 1).

Cholangioscopy can be done peroperatively, per-orally, or through percutaneous trans-hepatic route. The percutaneous route requires a large diameter, trans-hepatic tract that requires time to mature and is associated with risk of bile leak, bleeding, and tumor seeding along the tract. Hence, per-oral cholangioscopy is most popular that can be done directly via ultra-thin caliber endoscope or indirectly via the insertion of a cholangioscope through the accessory channel of the duodenoscope. Direct peroral cholangioscopy (DPOC) requires prior sphincterotomy/sphincteroplasty for the advancement of ultra-thin caliber endoscope. It is technically challenging due to the looping of the endoscope in the stomach and the lack of stability while advancing the endoscope through the biliary system. Hybrid balloon catheter anchoring device and double bending cholangioscope are the few of those technical modifications to overcome the challenges. Moreover, the risk of air embolism is present that may occur due to excessive gas pressure in thin caliber biliary system.<sup>12</sup> Advantages of DPOC include higher image resolution and higher caliber of the accessory channel. Image-enhanced endoscopy (IEE) during DSOC can help differentiate benign from a malignant tumor and define tumor margin by evaluating surface and micro-vasculature. Indirect cholangioscopy using mother duodenoscope and baby cholangioscope requires two operators, has highly fragile instruments, and is associated with high cost. It has fallen out of favor due to the above factors along with poor image resolution, provision of only two way deflection of cholangioscope tip, longer set up, and procedure time.<sup>12</sup>

### Single Operator Peroral Cholangioscopy

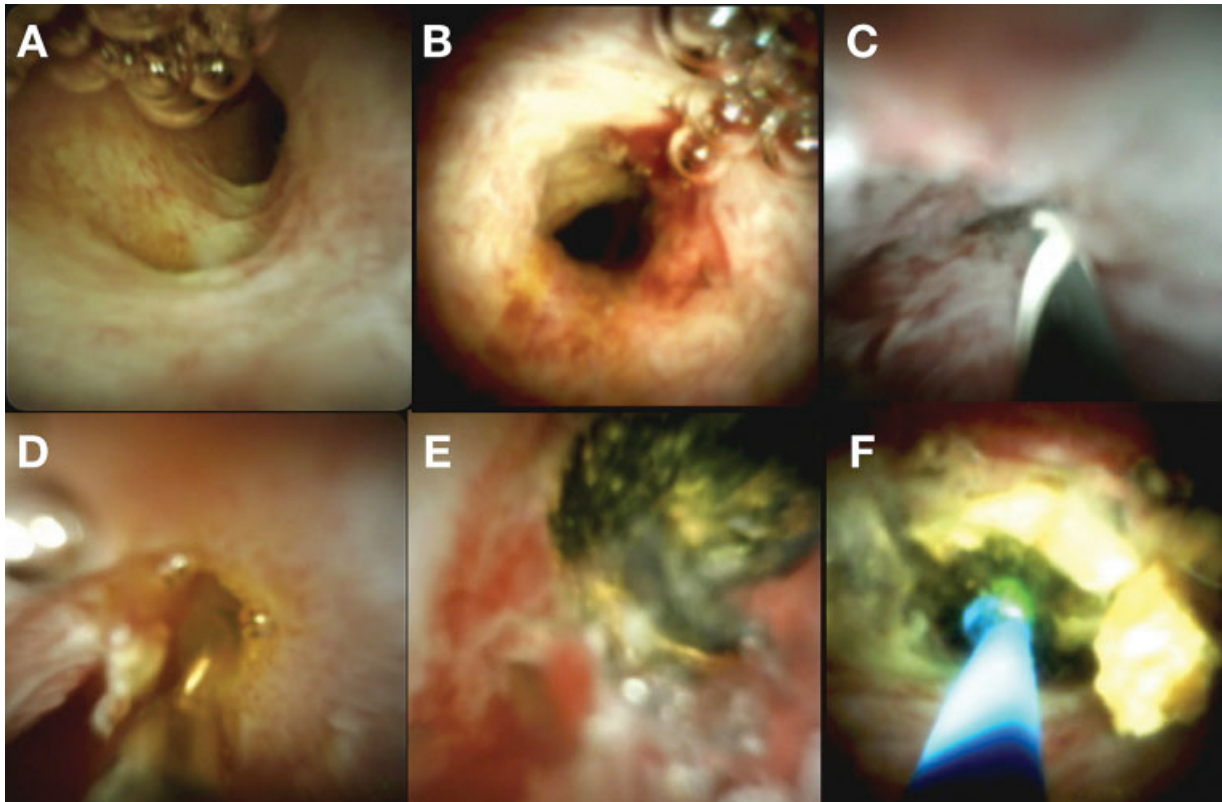
Single operator system initially consisting of the directable plastic sheath and a reusable fiber-optical light and image guide (Legacy SpyGlass, Boston Scientific, Marlborough, Massachusetts) have addressed some of the limitations of a dual operator system. It can be advanced into the biliary system with or without wire guidance by a single operator controlling the mother duodenoscope and 3.3 mm diameter baby cholangioscope. Cholangioscope has a four-way tip deflection and two channels (for irrigation and suction). This allows for higher maneuverability and passage of accessories such as biopsy forceps, endomicroscopy probe, snare, or basket allowing therapeutic procedures such as laser or electrohydraulic lithotripsy (EHL).<sup>12</sup> A prospective study from India has demonstrated that the visual impression of the SpyGlass is accurate in 89% of cases to differentiate benign from the malignant lesion, whereas targeted SpyBite biopsies are accurate in 82%, which is far higher than brushing cytology/blind biliary biopsy. Irregularly dilated tortuous vessels, papillary/villous projections, and nodularity/mass were the characteristics of a malignant lesion. A homogenous granular mucosa devoid of any mass and smooth surface without neovascularization were criteria for benign lesions.<sup>13</sup> In a series of five cases from India showed that SOPOC with intraductal ultrasound (IDUS) can be helpful in the evaluation and management of portal biliopathy when the cause of obstruction is not well defined by identifying pericholedochal collaterals, intraductal varices or ischemic stricture.<sup>14</sup>

### Digital Single Operator Cholangioscopy

Cholangioscopy was revolutionized using DSOC (SpyGlass DS, Boston Scientific) with disposable cholangioscope that captures images digitally. DSOC is superior to fiberoptic single operator cholangioscopy (FSOC) with regard to image quality, visualization and maneuverability, especially for targeting left intraductal lesion in a randomized novel cholangioscopy bench model study (→ Fig. 3).<sup>15</sup>

The advantages of DSOC include:

- (1) Feasibility of radiation-free ERCP
- (2) Direct visualization of the biliary system



**Fig. 3** SpyGlass DS single operator cholangioscopy. (A) Benign stricture on cholangioscopy showing smooth surface without neovascularization. (B) IgG4 related cholangiopathy-related stricture on cholangioscopy. (C) Nodularity and irregular vessels in a tight malignant stricture negotiated with catheter. (D) Spybite biopsy being taken during cholangioscopy. (E) Impacted stone is seen on cholangioscopy. (F) Stone fragmentation by laser lithotripsy.

(3) Tissue acquisition

(4) Cholangioscopy-directed therapy

Radiation-free ERCP could be valuable particularly in pregnant females as shown in a recent multicenter study, in which DSOC helped in avoiding fluoroscopy in 50% of cases.<sup>16</sup>

A multi-center randomized controlled study has shown higher sensitivity (68.2%) and accuracy (76.7%) of DSOC-guided tissue sampling compared with conventional ERCP-guided brush cytology (21.4% sensitivity, 59.3% accuracy) with similar adverse event profile in indeterminate biliary strictures.<sup>17</sup> Importantly, the visual impression on DSOC had a sensitivity of 95.5% with an overall accuracy of 87.1%.<sup>17</sup> This has important clinical implications as malignant-looking operable lesions on cholangioscopy can be offered surgery even if tissue sampling is inconclusive. An expert consensus statement has enumerated indications of peroral cholangiography: (1) targeted biopsy in indeterminate biliary strictures, (2) cholangioscopy-guided lithotripsy when standard techniques fail.<sup>18</sup> This has been substantiated by two recent large multi-center studies. The first one on cholangioscopy-guided tissue acquisition showed that cholangioscopic visual impression and tissue acquisition had an overall accuracy of 77.2% and 86.5%, respectively.<sup>19</sup> The second one showed that cholangioscopy-guided lithotripsy was effective in stone clearance in a single session in 80% of cases (among whom

80% had earlier failed ERCP), especially for less than 3 cm stones.<sup>20</sup> Latest consensus guidelines state that cholangioscopy-guided visualization and -guided biopsy during initial ERCP may reduce the need for multiple procedures in indeterminate strictures (except for distal biliary strictures) although it is associated with a higher risk of cholangitis than standard ERCP necessitating prophylactic antibiotics and adequate biliary drainage.<sup>21</sup>

#### Single Operator Pancreatoscopy

Single operator pancreatoscopy (SOP) has been used for the evaluation of indeterminate pancreatic duct strictures and intraductal papillary mucinous neoplasm (IPMN). Therapeutic interventions such as intraductal lithotripsy and even intraductal necrosectomy in walled-off necrosis (WON) have been described.<sup>22</sup> In a large single-center study ( $n = 41$ ), SOP helped in directed biopsy and classification in suspected IPMN and impacted clinical management in 76% by providing additional information or tissue diagnosis. Post ERCP pancreatitis occurred in 17%.<sup>23</sup>

SOP-guided electrohydraulic lithotripsy (EHL) and laser lithotripsy (LL) can achieve complete ductal clearance in 89.9% and a single session was required in 73.5% according to a large ( $n = 109$ ) retrospective analysis. More than three stones were independent predictors of multiple sessions.<sup>24</sup> In a retrospective cohort study comparing SOP-guided lithotripsy versus extracorporeal shock wave lithotripsy (ESWL),

SOP-guided lithotripsy was associated with the requirement of less number of sessions and more complete clearance with similar adverse event rates. Stones > 1 cm was associated with failure of SOP-guided lithotripsy.<sup>25</sup>

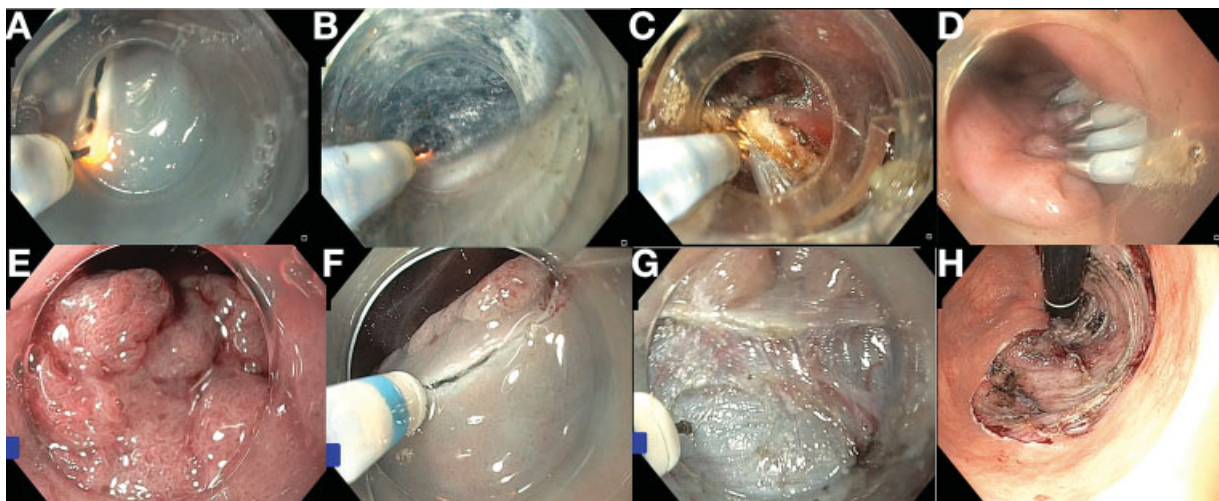
### Step Out of Gut Wall

#### Evolution of Third-Space Endoscopy

The scope of therapeutic endoscopy has increased manifold with the introduction of natural orifice trans-luminal endoscopic surgery (NOTES). This has enabled the entry of flexible endoscopy into the second- and third-space (peritoneal cavity and submucosal space respectively). One of the major concerns with third space endoscopy was secure closure of the mucosal defect. Sumiyama et al have shown the safety of submucosal endoscopy with mucosal flap safety valve (SEMF) in which entry into the peritoneal cavity was safely closed with mucosal flap.<sup>26</sup> Using the SEMF technique, Pasricha et al first performed endoscopic myotomy in an animal model in 2007.<sup>27</sup> Subsequently, Inoue performed the first human case of peroral endoscopic myotomy (POEM) in 2008.<sup>28</sup> The first case of submucosal tunneling and endoscopic resection (STER) for the submucosal tumor was also performed by Inoue in 2012.<sup>29</sup> Now, third-space endoscopy with SEMF is used in various GI disorders such as achalasia (POEM), sub-epithelial tumor (STER/peroral endoscopic tunneling: POET), refractory gastroparesis (gastric or G POEM), Zenker's diverticulum (Z-POEM), and esophageal stricture (POETRE-peroral endoscopic tunneling for restoration of the esophagus).<sup>26</sup> Among these, POEM is the most popular technique of third-space endoscopy with vast experience worldwide. Gastroesophageal reflux disease (GERD) is the Achilles' heel of POEM procedure as a treatment of achalasia. New novel modalities such as POEM with endoscopic fundoplication have been introduced to mitigate this issue which was first reported by Inoue et al.<sup>30</sup>

#### Peroral Endoscopic Myotomy

Peroral endoscopic myotomy (POEM) is the most extensively studied third-space endoscopic procedure. The steps are submucosal injection, mucosal incision, submucosal tunneling, myotomy, and mucosal incision closure (→ Fig. 4). Studies have shown excellent short and midterm results of POEM for achalasia but long-term results are scarce.<sup>26</sup> Also, 94% clinical success rate at 1 year has been reported in a prospective study of 200 achalasia patients undergoing POEM.<sup>31</sup> Subsequently the mid-term follow-up data (3 years) of 408 patients showed the highest clinical success at 3 years for type II achalasia (93.5%) followed by type I (87.5%) and type III achalasia (75%).<sup>32</sup> Similar efficacy and safety of POEM for prior treatment failure cases compared with treatment-naïve patients have been shown in an analysis of more than 500 patients.<sup>33</sup> Various technical issues such as anterior versus posterior myotomy and short (3 cm) versus long myotomy ( $\geq 6$  cm) have also been addressed by studies from India in randomized controlled trials. Anterior and posterior POEM had similar treatment efficacy where mucosectomies were more common in anterior POEM, whereas GERD was more common in posterior myotomy due to disruption of sling fibers.<sup>34</sup> Short myotomy was shown to have similar success rates, adverse events, and GERD in type I and II achalasia with significantly shorter operating times.<sup>35</sup> Type III achalasia requires long myotomy. Most of the adverse events are insufflation-related (e.g., pneumoperitoneum) that do not require active intervention and can be managed during the procedure without untoward consequences.<sup>31</sup> Early recognition of bleeding points and hemostasis can be done by red dichromatic imaging (RDI).<sup>36</sup> A novel multipurpose bipolar device can help obviate the need for a change of accessories in third space endoscopy as shown in a series of 10 cases which included seven cases of achalasia.<sup>37</sup> POEM was also shown to be an effective and durable treatment for spastic esophageal motility disorders (Type III achalasia, Jackhammer esophagus, distal esophageal spasm- DES) with long term (5 years) success rate of 82.6%.<sup>38</sup>



**Fig. 4** Third-space endoscopy A–D: steps of POEM. (A) Mucosal incision. (B) Submucosal tunneling. (C) Myotomy. (D) Mucosal incision closure. (E–H) Endoscopic submucosal dissection (ESD). (E) Laterally spreading rectal tumor seen on a narrow band imaging near focus. (F) Mucosal incision. (G) Submucosal dissection. (H) Tumor bed after complete resection: turned out to be high-grade dysplasia.

Most cases of post POEM GERD have been shown to be mild and proton pump inhibitor (PPI) responsive. None of the procedure-related factors can predict post POEM GERD.<sup>39</sup> Identifying the twin penetrating vessels during myotomy can help prevent disruption of oblique fibers and thus GERD.<sup>40</sup> Other novel technique to reduce reflux was simultaneous endoscopic fundoplication (POEM-F).<sup>41</sup> Post POEM heartburn can occur due to acid fermentation, delayed esophageal clearance, stasis, and esophageal hypersensitivity other than true acidic reflux.<sup>42</sup>

### Third Space Endoscopy beyond POEM

Large (>3 cm), submucosal tumors arising from muscularis propria can have malignant potential and can be resected endoscopically by submucosal tunneling and endoscopic resection (STER). The steps are similar to POEM except for tumor dissection and en bloc removal by snare instead of the myotomy.<sup>26</sup> In a large series of 44 patients from India reported 99.7% technical success and 88.4% en bloc tumor removal with STER. Minor adverse events occurred in 16.9% without any major adverse events. Leiomyoma and gastrointestinal stromal tumors (GIST) are the most common submucosal tumors resected. There was no difference in recurrence rate among those with piecemeal or en-bloc resection (►Fig. 4).<sup>43</sup>

Gastric POEM with pyloromyotomy can be helpful in refractory gastroparesis when pylorospasm is the main pathophysiologic mechanism. It has comparable efficacy as laparoscopic pyloromyotomy with lower postoperative morbidity according to a prospective matched control study.<sup>44</sup>

Z-POEM for Zenker's diverticulum can reduce the risk of perforation compared with conventional myotomy as the mucosa is preserved in D-POEM.<sup>26</sup> Division of epiphrenic diverticulum (D-POEM) has been described by a single-center study from India in 13 patients with three quarters having associated motility disorder. It was effective in all cases with a single report of the major adverse event warranting surgery.<sup>45</sup>

### Conclusion

The journey of the endoscopist in reaching out to the inaccessible areas in the GI tract has been remarkable. Substantial progress in GI endoscopy and technological evolution has led to improvement in techniques of deep enteroscopy, cholangiopancreatography, and third-space endoscopy. Deep enteroscopy has now evolved from balloon-assisted enteroscopy to novel motorized spiral enteroscopy, which has made pan-enteroscopy a reality in the majority of cases. Cholangiopancreatography has improved the evaluation of indeterminate biliary or pancreatic duct strictures with complete stone clearance in difficult cases. Third-space endoscopy is replacing surgical and other endoscopic management techniques in various GI disorders such as achalasia, refractory gastroparesis, subepithelial tumors, Zenker's, and epiphrenic diverticulum, and difficult esophageal strictures. The results of such newer modalities have so far been promising and reassuring. The future possibilities are never-ending as we push the limits of endoscopic innovation in reaching the inaccessible.

### Authors' Contributions

Conceptualization: MR and PP; Literature review and writing original draft: PP and MR, Illustrations: IP and APS; Images: IP and APS; proofreading and critical review: PP, MR, DNR, IP, and APS, approving final manuscript: MR, PP, IP, APS, and DNR.

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### Conflict of Interest

None declared.

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